The synthesis of novel analgesics based on the morphine prototype

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THE SYNTHESIS OF NOVEL ANALGESICS BASED ON THE MORPHINE PROTOTYPE

submitted by

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CONTENTS

Abstract

Morphine-6-glucurinde is a more effective and longer lasting analgesic than morphine, with fewer side effects. Unfortunately, it well documented that the coupling proceedure between morphine and glucuronic acid is a problematic one. This has led Lacy and Sainsbury to consider isosteres of M6G, where the oxygen linkage between the two moieties is replaced by a CH_2 unit. In a continuation of this work, we have attempted to utilise free radical chemistry to achieve this coupling.

We also report on the synthesis of some 6β-alkyl codeine derivatives by reduction of alkenyl codeines derived from dihydrocodeinone via Wittig chemistry. These compounds have shown activity comparable to the parent compound, codeine, in the mouse hot plate test.

Increased rigidity of ring C, as seen in Diels-Alder adducts of thebaine (**3**), assists in increasing opioid activity. We have attempted to fuse a new ring system to position C-7 and C-8 of the morphine skeleton. Initial attempts to use the Robinson annulation to form this new ring system have proved largley unsuccessful. However, an alternative route using Diels-Alder reactions have afforded several novel compounds.

The benzene address moiety in NTI (**43**) and SIOM (**66**) play an important role in determining their selectivity at the opioid receptor. NTI and SIOM are both potent, δ-selective ligands despite the fact that the benzene address is held rigidly in different conformations, co-planar in NTI and orthogonal to the plane in SIOM with respect to ring C. In an attempt to explore further the conformational requirements of the so called address moiety, we have synthesised successfully compound **82** in which the benzene ring is 90° to the plane of ring C.

Acknowledgements

The work described in this thesis was carried out in the Organic Chemistry Department of the University of Bath between October 1994 and September 1997. Financial support (CASE award) and generous gifts of compounds from MacFarlan Smith Ltd. is greatly acknowledged.

I am most grateful to Professor Malcolm Sainsbury, my supervisor, for his help and enthusiasm; his constant source of ideas and for allowing me the freedom to explore my own avenues. I must also thank my industrial supervisor Dr. Mike McPherson for his interest, useful discussions, and for arranging a stay in Edinburgh during the Edinburgh festival 1997. I also thank everyone at MacFarlan Smith for making my visit enjoyable and memorable.

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Abbreviations

Ac	acetyl
AIBN	azobisisobutyronitrile
Arg	Arginine
ax	axial
BNI	binaltorphimine
br	broad
CI	chemical ionisation
CNS	central nervous system
COSY	correlated spectroscopy
CPM	cyclopropylmethyl
δ	delta
d	doublet
DCM	dichloromethane
DEAD	diethylazodicarboxylate
DEPT	distortionless enhancement by polarization transfer
DMF	*N,N*-dimethylformamide
DPDPE	[D-Pen^2, D-Pen^5]enkephalin
EI	electron impact
eq	equitorial
FAB	fast atom bombardment
β-FNA	β-funaltrexamine
gem	geminal
Gly	glycine
GPI	guinea pig ilium
HOMO	highest occupied molecular orbital
ICI174864	(Allyl)$_2$Tyr-Abi-Abi-Phe-Leu-OH
Ile	isoleucine
IR	infra red
J	coupling constant
κ	kappa
LDA	lithium diisopropylamide
Leu	leucine
LUMO	lowest unoccupied molecular orbital

μ	mu
m	multiplet
MeOH	methanol
Met	methionine
M3G	morphine-3-glucuronide
M6G	morphine-6-glucuronide
MHz	megahertz
Mp	melting point
MVD	mouse *vas deferens*
MVK	methylvinyl ketone
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser enhancement
NTB	naltriben
NTI	naltrindole
OMI	oxymorphindole
Phe	phenylalanine
R_f	retention factor
σ	sigma
SINTX	spiroindanylnaltrexone
SIOM	spiroindanyloxymorphinone
SKF	Smith Kline French
SOMO	single occupied molecular orbital
t	triplet
TBAF	tetrabutylammonium fluoride
TCNE	tetracyanoethylene
Tf	trifluoromethane sulphonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TPP	triphenylphosphine
p-TsOH	*para*-toluene sulphonic acid
Tyr	tyrosine
UDP	uridine diphosphate

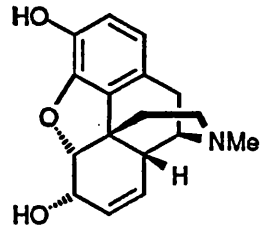
CHAPTER 1

INTRODUCTION

1.1. The Opium Alkaloids

Opium, the sun-dried extract obtained from the incised unripe capsules of *Papaver somniferum*, has been used for centuries as a narcotic agent and a pain killing substance. Crude opium contains a complex mixture of almost twenty-five alkaloids. The principle alkaloid, and the one chiefly responsible for analgesic activity is morphine (**1**), named after Morpheus, the Greek God of dreams. It was first isolated in the pure form in 1805 by the German pharmacist, Friedrich Sertürner[1].

Although the functional groups present in morphine had been identified by 1881, it was many years later that Gulland and Robinson finally established the now accepted structure of morphine[2]. The first total synthesis of morphine was achieved in 1952 by Gates and Tschudi[3, 4]. The biosynthetic pathway to the alkaloid has also been established and this work is well documented[5, 6].



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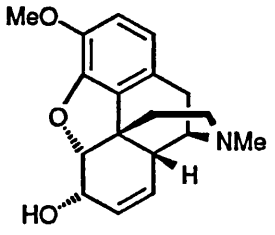

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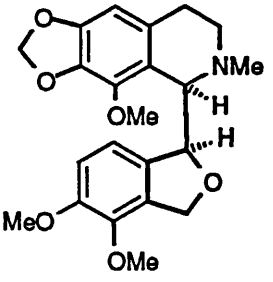

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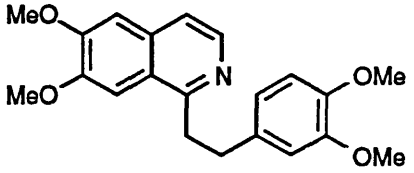

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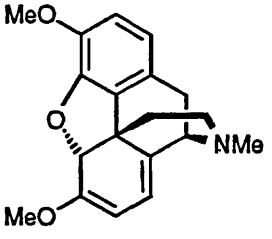

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Opium also contains several other minor alkaloids of therapeutic importance. These include codeine (**2**), the 3-*O*-methyl ether of morphine, noscapine (narcotine, **3**), papaverine (**4**) and thebaine (**5**).

1.2. Nomenclature and Stereochemistry

The structure of morphine consists of five distinct ring systems (**Figure 1**): phenolic **A**, cyclohexane **B**, cyclohexenol **C**, *N*-methyl-piperidine **D** and a partially saturated furan ring **E**. Morphine lends its name to a the morphinan family of alkaloids and has a full systematic name of 7,8-didehydro-4,5-epoxy-*N*-methyl-(5α,6α)-morphinan-3,6-diol.

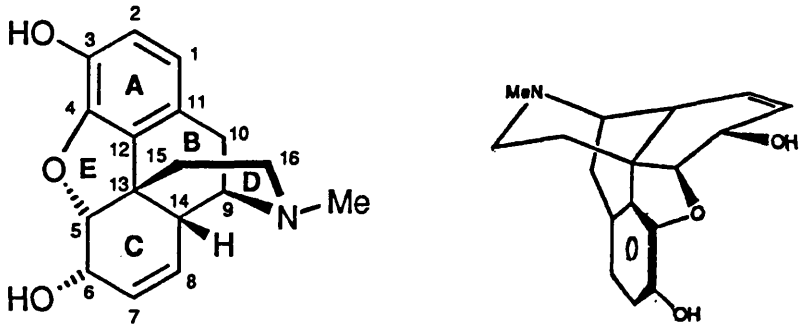


Figure 1

The absolute stereochemistry of morphine was unambiguously determined by Mackay and Hodgkin in 1955 from an X-ray crystallographic analysis of morphine hydroiodide dihydrate[7]. Morphine and its analogues are approximately T-shaped with the atoms of ring **A, B** and **E** lying in one plane, and the atoms of ring **C** and **D** in a second plane at right angles to the first.

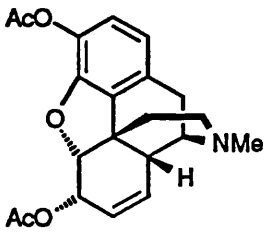
The **B/C** ring junction is *cis* fused. Ring **C** is almost boat shaped in the crystal form, while the nitrogen containing ring, **D**, adopts an almost regular chair conformation with the methyl group attached to nitrogen via an equatorial bond. The C-5 oxygen and the C-6 hydroxyl group are *cis* to each other.

Natural (-)-morphine contains asymmetric centres at carbons 5(R), 6(S), 9(R), 13(S) and 14(R) and it is this precise geometric arrangement which affords the familiar opioid pharmacological activity. (+)-Morphine, with the opposite geometry at each of the five asymmetric centres, is devoid of analgesic activity[8].

1.3. Morphine Analogues - The Search for Improved Opioid Analgesic Drugs

Morphine is still one of the best and most effective cheap analgesics available to man. It is used in the treatment of 'deep' chronic pain rather than 'sharp' periodic pain. Morphine exerts its pharmacological actions on the central nervous system and appears to work by interacting with receptors in the brain to elevate the pain threshold.

Unfortunately, morphine also induces many undesirable side-effects including respiratory depression (death by morphine overdose is almost always as a result of respiratory collapse), drowsiness, nausea and vomiting. Repeated use produces tolerance so that the amount of drug required to obtain the same degree of relief becomes increasingly greater. Furthermore, continued use of morphine results in the development of physical dependence and cessation induces symptoms of withdrawal (abstinence syndrome). The sense of euphoria on morphine administration has led to its social use and eventual abuse.



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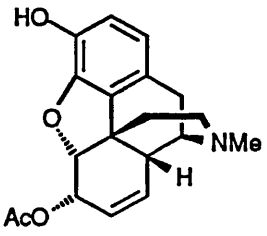

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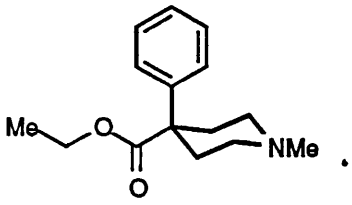

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Over the years a wealth of research has taken place in an attempt to divest morphine of its side-effects. One of the earliest attempts involved acetylation to give 3,6-diacetylmorphine, or heroin (6). In 1898, heroin was introduced into clinical medicine as a drug superior in potency to morphine without its addictive character. However, the faulty nature of this claim was soon realised. It is now known that the faster onset of action and the 2-3 fold greater potency of the drug in man are due to increased lipophilic character and the ability of heroin to cross the blood-brain barrier more readily than morphine. *In vivo*, heroin is metabolised to 6-acetylmorphine (7)

and morphine. As heroin itself does not bind to the opiate receptor[9], it has been proposed that its actions are due to these two metabolites

In the late 1930's the search for a synthetic substitute for atropine (a antispasmodic muscle relaxant) culminated serendipitously in the discovery of meperidine (pethidine, **8**), the first non-opioid derived analgesic with a much simpler structure than morphine[10]. This led to the belief that the true pain killing pharmacophore was less complex than morphine itself and the so called 'morphine rule' was proposed (**Figure 2**). This stated naively that, for analgesic activity, compounds must possess (i) an aromatic ring attached to (ii) a quaternary carbon atom and (iii) a tertiary amino group situated two carbon atoms farther away.

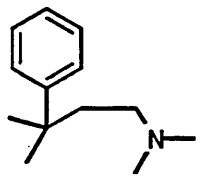
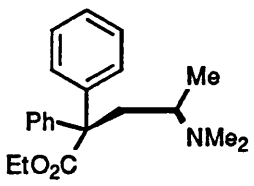


Figure 2

Methadone[11] (**9**), synthesised in 1946, is an example of a drug fulfilling these criteria. It possesses pharmacological properties similar to those of morphine. The abstinence syndrome of methadone is slower in onset, lasts longer but is less intense than that experienced with morphine. For these reasons, and because of its oral effectiveness, methadone has found use in the treatment of drug addicts to wean them off morphine (or heroin).



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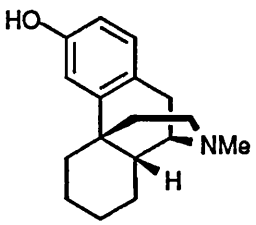

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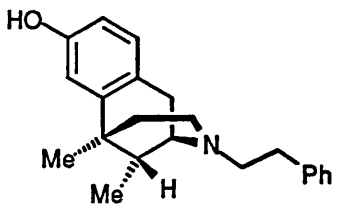

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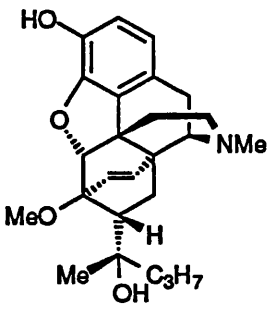
By the mid-1950's further 'simple' morphines, exemplified by levorphanol (**10**) and phenazocine (**11**), were synthesised. Levorphanol, a morphinan, is about four times more potent than morphine and induces fewer side-effects at optimal doses either orally, or parenterally. Since levorphanol is not metabolised in the liver to the same extent as morphine, it also provides analgesia for up to 8 hours. Phenazocine[12], a benzomorphan, is also an effective analgesic for most types of severe pain at a parenteral dose of 1-3mg. It is also active orally and is used in the treatment of chronic pain at a dose level of 2-5mg. Tolerance develops more slowly to the effects of phenazocine, compared to morphine, and it also appears to be less addictive. The morphinans and benzomorphans are only effective if they possess the same absolute stereochemistry as morphine.

For a good few years the trend was therefore to snip away at the morphine skeleton in an attempt to achieve a more efficacious analgesic. However, this process of simplification, which leads to more conformationally flexible products, was challenged by Bentley in the early 1960s.

Bentley and co-workers argued that if morphine and related compounds bind to receptors in order to initiate their responses, molecular flexibility would permit a molecule to adapt to a number of receptor types. This mobility would not only elicit the desired analgesic response, but in addition, the unwanted side-effects. He therefore reasoned that alkaloids more complex and, in particular, of greater rigidity than morphine might bind to the opiate receptor with more selectivity and thereby result in agents with superior analgesic properties, free of undesired side-effects. Although present knowledge of opioid receptors suggests that such a view is now an oversimplification of the situation, this novel approach more than 30 years ago led to the synthesis of a new class of compounds known collectively as the oripavines, derived from the dienic alkaloid thebaine (**5**) by Diels-Alder chemistry[13].



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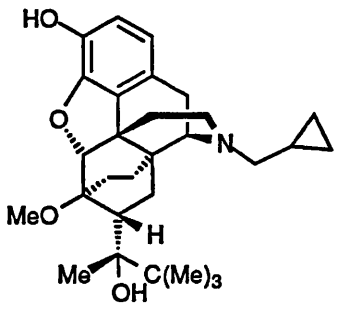

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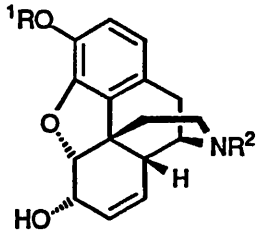
Of particular interest in this series is etorphine (**12**) which is approximately 10,000 times more potent than morphine[14]. The effect is due to the fact that it is a very hydrophobic molecule and can pass through the blood-brain barrier 300 times more easily than morphine, as well as its greater affinity for the analgesic receptor site due to better binding interactions. Unfortunately this potency is not translated into selectivity, and because of this its use has been restricted to veterinary medicine. However, a related compound buprenorphine (**13**), with low levels of dependence and respiratory depression, is used clinically for the control of moderate to severe pain[15].

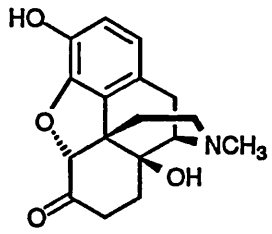
1.4. Opioid Antagonists and Mixed Agonist-Antagonists

The change from opiate agonist to antagonist, or mixed agonist-antagonist, on replacing the *N*-methyl group of morphine analogues with an allyl unit was first observed with *N*-allylnorcodeine (**14**) in 1915. *N*-Allylcodeine reverses the decrease in respiratory rate caused by morphine, *i.e.* it behaves as an antagonist of morphine. The significance of this finding was not fully realised until *N*-allylnormorphine (nalorphine, **15**)[16] was synthesised and tested. Pharmacological data revealed that nalorphine, which provides an effective antidote for morphine overdose, also induces analgesia at a dose level comparable to morphine in man. However, its clinical acceptance as an analgesic agent was hampered due to psychotomimetic effects associated with its use.

The observation that a drug could have antagonist activity and still retain potent analgesia, *i.e.* act as a mixed agonist-antagonist or dualist, was extremely important and stimulated an intensive search for other such agents. Modification of the *N*-substituent indicated that for optimum antagonist activity a straight chain of three carbons is required. Extending the chain by one carbon lowers activity, whereas a five-carbon chain or slightly more restores agonist activity. Morphine derivatives with aromatic side-chains, such as *N*-phenethylnormorphine (**16**), have also been shown to behave as antagonists, in addition to exhibiting analgesic activity.



14 R^1=CH_3; R^2=CH_2CH=CH_2
15 R^1=H; R^2=CH_2CH=CH_2
16 R^1=H; R^2=$CH_2CH_2C_6H_5$



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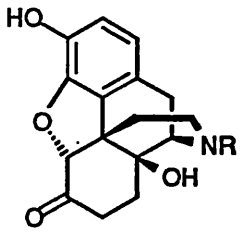


18 R=CH_2CH=CH_2
19 R=H_2C— 
20 R=H_2C— 

The fact that oxymorphone (**17**) is a more potent agonist than morphine, led Fishman and Lewenstein to synthesise its *N*-allyl derivative. The hope was that this compound might prove to be more potent than nalorphine yet show less of its undesirable effects. Indeed, *N*-allylnoroxymorphone (naloxone, **18**) was subsequently found to be 10-20 times more potent than nalorphine, as an antagonist but more importantly it did not possess any agonist activity of its own *i.e.* it is a pure antagonist. Analogues of naloxone with cyclopropylmethyl (naltrexone, **19**) or cyclobutylmethyl (nalbuphine, **20**) groups were also shown to be antagonists of increased activity, but they exhibit some agonistic action.

1.5. Opioid Receptor Theory

1.5.1. Beckett-Casy Hypothesis

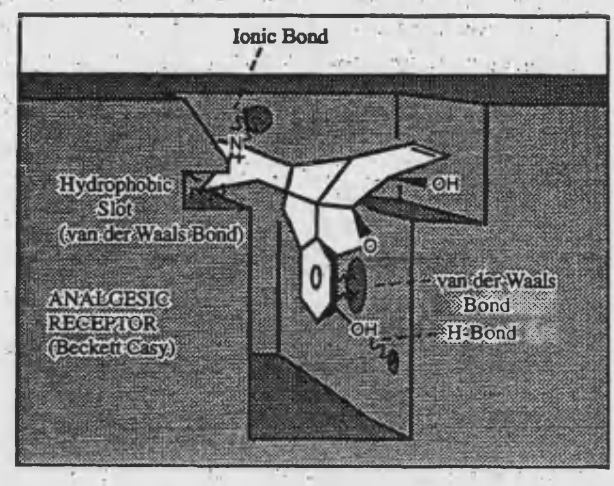


Figure 3

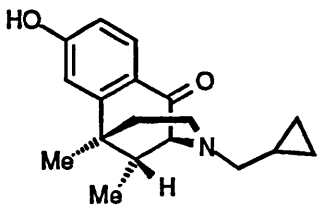
The original concept of an opioid receptor was first postulated in 1954 by Beckett and Casy[17]. The theory was based on stereochemical evidence and structural features common to analgesics known at the time. Using natural (-)-morphine as a model, because of its rigid structure, the authors considered that the 'active features' on the opiate ligand should complement or 'fit' the active sites on the receptor surface. It was therefore proposed that the receptor has three key recognition sites:

1. a flat portion that allows binding with the aromatic ring of the analgesic drug through van der Waal type forces.
2. an anionic site that associates with the positively charged basic centre of the ligand.
3. a cavity suitably orientated with the two sites above to accommodate the projecting bimethylene (C-15, C-16) portion of the piperidine ring D that lies in front of the plane containing the aromatic ring and the basic centre.

The model adequately accommodates most structural variants of morphine as well as morphinan and benzomorphan ligands possessing the same absolute configuration. However, many other anomalies existed which could not be accounted for by such a simple single receptor model.

1.5.2. Multiple Opioid Receptors

The first conclusive evidence for the existence of multiple opioid receptors was provided by Martin and co-workers in 1976[18]. In behavioural studies performed on the chronic spinal dog, differences in pharmacological responses to different narcotic analgesics and their inability to substitute for each other in suppressing withdrawal symptoms led them to postulate the existence of three distinct types of receptors. The receptors were named after the prototype drugs used in the studies: μ for morphine (**1**), κ for ketazocine (**21**), and σ for SKF 10,047 (*N*-allylnormetazocine, **22**). However, it is now known that the σ receptor is not opioid in nature[19].



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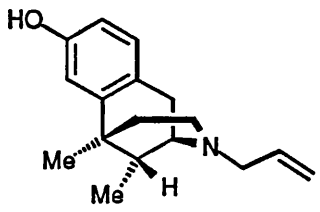

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Following the discovery of the enkephalins[20] (*vide infra*), Kosterlitz's group provided evidence for a further receptor type[21]. They found that electrically stimulated contractions of the isolated guinea pig ileum (GPI) were much more sensitive to inhibition by morphine and related opiate alkaloids than by enkephalins, whereas the opposite was observed with the mouse *vas deferens* (MVD). They suggested that the two bioassay systems contained different receptor populations. The major receptors present in the GPI prefer opiates and resemble μ receptors, whereas

the *vas deferens* contain a preponderance of receptors that exhibit a higher affinity for enkephalins and their analogues. These receptors were named δ (*deferens*) receptors.

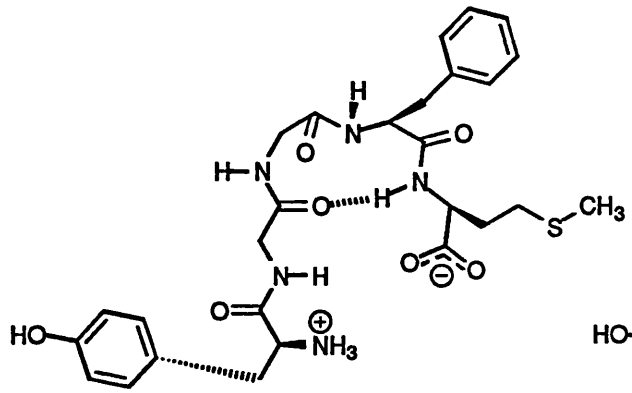
The reputed effects mediated by the three main opioid receptor types are shown in **Table 1.** There is now evidence for subtypes of μ, κ and δ receptors, *i.e.* μ_1 and μ_2, κ_1, κ_2 and κ_3, and δ_1 and δ_2 have been reported.

Receptor	Response on activation
μ (mu)	analgesia, respiratory depression, euphoria, reduced gastrointestinal movement
κ (kappa)	analgesia, dysphoria, pychomimetic effects, respiratory depression
δ (delta)	analgesia

Table 1

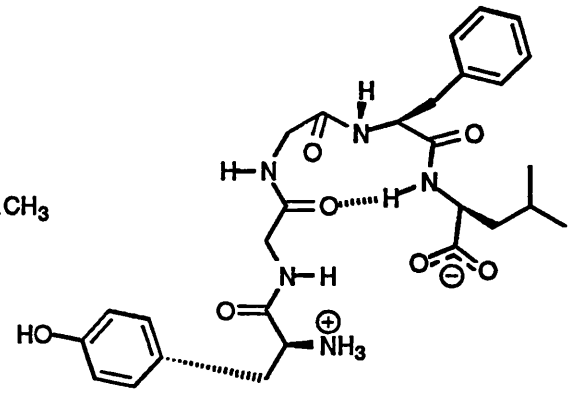
1.6. The Endogenous Opioid Peptides

The characterisation of biological receptors in mammalian brain tissue instigated the search for an 'endogenous opioid' as it was considered unlikely that these receptors would have evolved solely for interaction with ligands exogenous to the body. In 1975, Hughes and Kosterlitz[20] isolated extracts from pig brain which had opioid activity similar to that of the opiate alkaloids. This activity was shown to be due to a mixture of two peptides which were characterised and named Met-enkephalin (**23**) and Leu-enkephalin (**24**).



Tyr-Gly-Gly-Phe-Met

23 Met-enkephalin



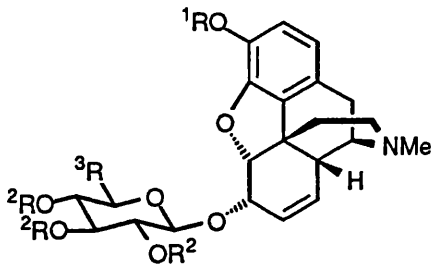
Tyr-Gly-Gly-Phe-Leu

24 Leu-enkephalin

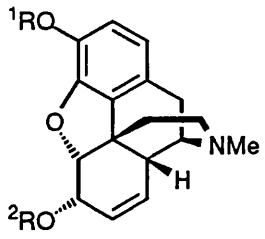
The two enkephalins are pentapeptides which differ in a single residue at the C terminus. The opioid peptides are formed by the proteolytic cleavage of three inactive protein precursors, proopiomelanocortin, proenkephalin and prodynorphin.

The enkephalins are metabolised rapidly *in vivo* primarily by two peptidases, enkephalinase A, which splits the Gly-Phe bond and enkephalinase B, which splits the Gly-Gly bond. It is this facile hydrolysis of the peptide bonds which limits the use of enkephalins as effective analgesics. From structural activity relationship studies, it has been shown that both the phenol ring and amino group of the tyrosine residue are essential for opioid activity. As the tyrosine fragment also forms an integral part of the morphine skeleton there have been suggestions that the activity of morphine is due, in part, to this tyrosine residue acting as a mimic of the same unit in enkephalin. Some authors have been tempted to overlay the peptides on a model of morphine, thus to suggest that this is the conformation they present at the receptor site.

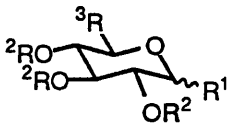
1.7. Metabolites of Morphine



25 $^1R=^2R=H$; $^3R=CO_2H$
26 $^1R=Me$; $^2R=H$; $^3R=CO_2H$
27 $^1R=^2R=Ac$; $^3R=CO_2Me$



28 $^1R=Ac$; $^2R=H$
29 $^1R=\beta$-D-glucuronyl; $^2R=H$
30 $^1R=^2R=\beta$-D-glucuronyl



31 $^1R=\beta$-OH; $^2R=H$; $^3R=CO_2H$
32 $^1R=\alpha$-Br; $^2R=Ac$; $^3R=CO_2Me$
33 $^1R=OC(NH)CCl_3$; $^2R={}^i$PrCO; $^3R=CO_2Me$

Morphine is subject to enantio- and regioselective glucuronidation catalysed by liver microsomal UDP-glucuronosyltransferase[22]. Conjugation with glucuronic acid (**31**) is the major pathway of metabolism for morphine and the route accounts for two-thirds of administered morphine recovered in urine[23].

The widely held view that only a single monoglucuronide, morphine-3-glucuronide (**29** , M3G), is produced in man[24] was dispelled nearly thirty years ago when morphine-6-glucuronide (**25** , M6G) was isolated, in trace amounts, from patients administered with morphine[25]. Glucuronides of drugs have high water solubility, are rapidly excreted from the body and are generally regarded as pharmacologically inactive[26]. Indeed, M3G is devoid of analgesic activity[24] although more recent reports[27] have suggested that M3G is able to antagonise the effects of both morphine and M6G.

Pharmacological studies carried out in 1971 by Japanese workers on M6G revealed that this minor metabolite, in contrast, is a potent analgesic[28]. After subcutaneous injection, M6G was reported to be approximately four times as potent as morphine with twice the duration of action in the mouse hot plate test, while after intracerebral administration it was 45 times more potent than the parent drug. The relatively small quantities of M6G available for further investigation impeded much

research into its properties over the next decade and few reports appeared in the literature during this period.

Renewed interest in the morphine metabolites came in the late 1980's when Osbourne and his co-workers published a brief communication highlighting the analgesic activity of M6G in six human cancer patients[29, 30]. Further detailed studies showed that M6G caused fewer gastrointestinal (*e.g.* sedation, nausea, vomiting) and respiratory side effects associated with normal morphine administration[31]. There is evidence to suggest that analgesia associated with M6G is mediated through the μ-type receptor[32], although enhanced binding to δ-receptors has also been reported. Of interest is the ability of M6G to cross the blood-brain barrier[33]. The phenomenon has been ascribed to its ability to exist in a folded, more lipophilic form, particularly in media of low-polarity such as biological membranes[34].

The emerging wealth of evidence suggesting that M6G, may in fact be the 'prodrug' of morphine, has stimulated interest in the use of M6G as a therapeutic agent in its own right. However, for the benefits to be fully realised, a simple synthetic route to the morphine metabolite is required which in turn can be adopted on a large scale.

To date, several syntheses of M6G have been reported. Yoshimura *et al.* have utilised the Koenigs-Knorr reaction in the coupling of 3-acetylmorphine (**28**) and acetobromide derivative of glucuronic acid (**32**)[35, 36]. The adduct **27** after subsequent deprotection affords M6G. Codeine-6-glucuronide (**26** , C6G) was obtained in essentially the same fashion. Scheinmann and co-workers at Salford Ultrafine have reported an alternative method using the enzyme β-glucuronidase as a catalyst in the selective hydrolysis of morphine-3,6-di-β-D-glucuronide (**30**, M3,6diG) to M6G[37]. A patent application by the same authors[38] also claim that M6G can be obtained by reaction of the imidate **33** with 3-acetylmorphine (**28**). Difficulties encountered by past members of our group in reproducing the results of both Yoshimura and the patent application have led to a modified synthesis of M6G by Lacy and Sainsbury[39] based on a significantly improved procedure for coupling **28** with 2α-

bromoglucuronate **32.** The complications experienced by Lacy are corroborated by similar reports by Carroll *et al.*[40] in their recent synthesis of **30.**

1.8. Recent Design Approaches to Selective Opioid Receptor Ligands

The universal opioid antagonists naloxone **(18)** and naltrexone **(19)** have been widely employed as tools in research. Indeed, their ability to antagonise an agonist effect is the key criterion employed for establishing the involvement of an opioid receptor mechanism. Since these antagonists interact with all three major opioid receptor types (μ, δ and κ) their usefulness in elucidating the effects mediated by a single receptor type is limited. Naltrexone is superior to naloxone as an antagonist because of its greater potency and bioavailability and for these reasons many of the approaches to developing selective non-peptide opioid antagonists over the past decade have involved the chemical modification of naltrexone. Rationales for the design of naltrexone derived selective antagonists have centred on the use of the bivalent ligand model and message-address concept.

1.8.1. Bivalent Ligand Approach[41]

The term 'bivalent ligand' is defined broadly as a molecule that contains two pharmacophores linked through a spacer[42]. The expectation of enhanced potency of a bivalent ligand over the monovalent analogue was based on a model in which recognition units of a bivalent ligand molecule bridge two neighbouring opioid recognition sites. The neighbouring sites may be located on a single opioid receptor system or on two associated receptors.

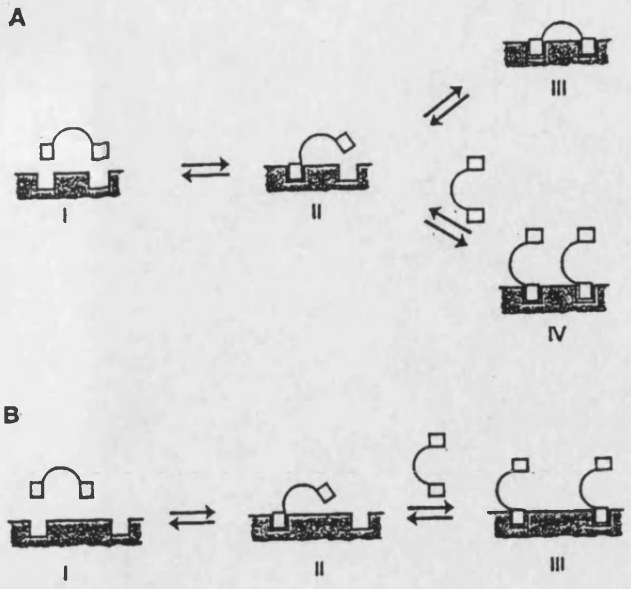
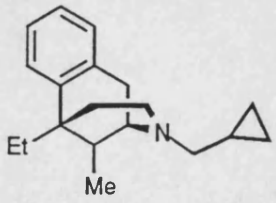


Figure 4 : The hypothetical case depicting the interaction of a bivalent ligand with neighbouring recognition sites on two receptor subtypes (A and B). In receptor type A, bridging of the bivalent ligand proceeds via the univalently bound state (II) to the totally bound state (III) which is favoured over occupation by two ligands (state IV). For receptor type B, only the univalently bound bivalent ligand state (II and III) is possible because the spacer does not allow bridging of neighbouring sites.

The potency increase should be substantially greater than a statistical factor of two as the free pharmacophore of a univalently bound bivalent ligand is confined within the locus of the vacant neighbouring recognition site. This would be equivalent to a very high concentration of pharmacophore (**Figure 4, state II**). Consequently bivalent binding (**state III**) should be favoured over univalent binding (**state IV**) if the spacer length permits bridging of the neighbouring sites. The simultaneous occupation of two recognition sites (**state III**) leads to selectivity. Since it is possible, however, that opioid receptor subtypes posses different inter-receptor distances, high selectivity for a single subtype (μ, δ or κ) may be achieved by incorporation of a specific spacer length into the bivalent ligand.



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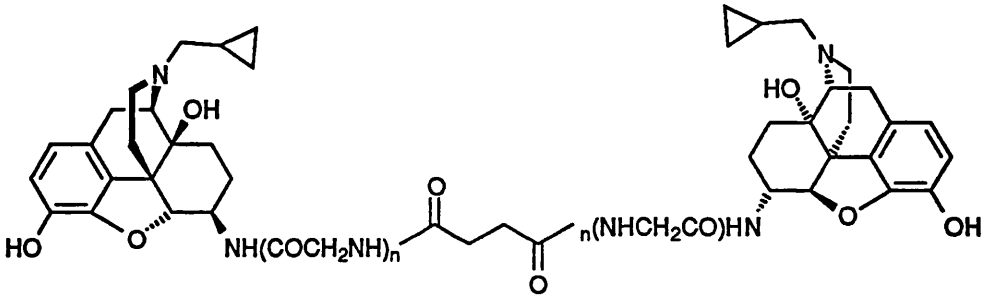
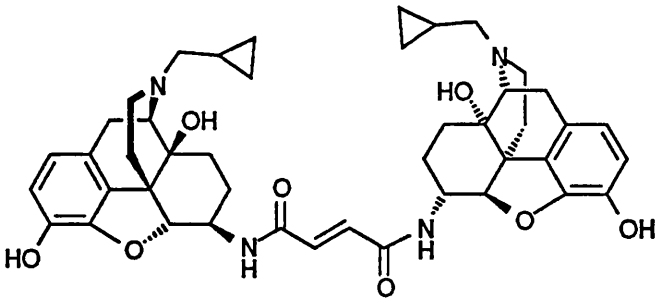
Studies evaluating the role of the spacer length on opioid antagonist selectivity were initially carried out on guinea pig ileum (GPI) preparations which contain μ- and κ-opioid receptors[43]. For bivalent naltrexone ligands (series **35**) containing glycyl spacers whose length could be varied (n=1-4), peak antagonism of morphine (μ-receptor selective agonist) was observed with a spacer containing 4 (n=2) glycyl units whilst maximum antagonism of ethylketazocine (**34**), a κ-receptor selective agonist, was observed at the shortest spacer length (n=0). The increase in antagonist potency at μ-receptors is consistent with either the bridging of two neighbouring receptor sites or two neighbouring subsites on a single μ-opioid receptor. Replacement of one of the pharmacophores in **35** (n=2) with (+)-naltrexone, inactive as an opioid antagonist, to give the (-)-(+)-isomer (*meso*) significantly reduced antagonist potency indicating that the neighbouring site has an enantio-preference of an opioid receptor site[44].



35 (n=1-4)

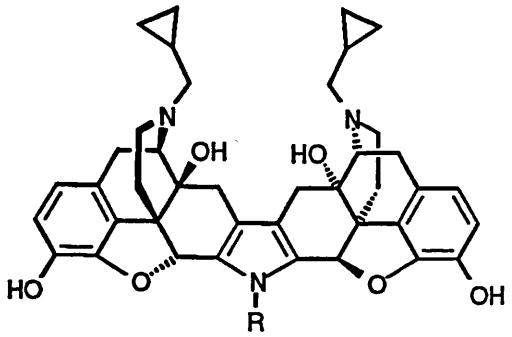


36

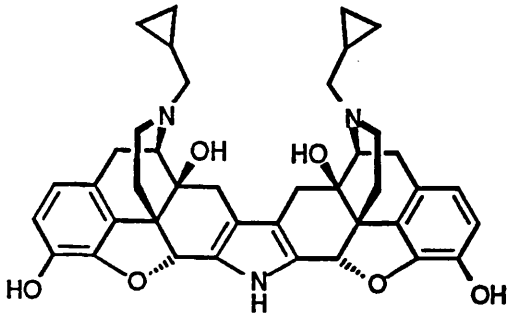
Substitution of the succinyl group in the potent κ-receptor antagonist **35** (n=0) with a fumaryl unit (**36**) resulted in the loss of κ-receptor selective antagonism. This

suggested that the relative orientation of the two pharmacophores is important in the recognition process. The observations led to the investigation of bivalent ligands with pharmacophores immobilised by a short rigid spacer, because it was considered that immobilisation of the antagonist pharmacophores in the correct orientation might facilitate bridging of the neighbouring recognition sites.

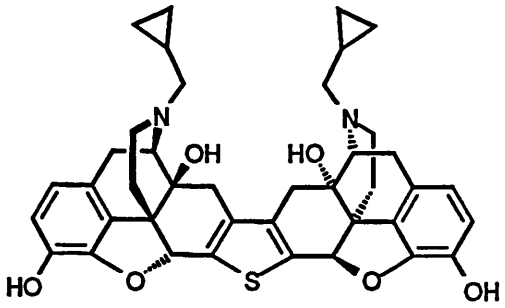
Pyrrole was selected as spacer on the basis of its accessibility and its ability to 'freeze' the orientation of both pharmacophores through ring fusion with the morphinan structure. The first two members of the series, synthesised under modified Pilloty-Robinson conditions, were norbinaltorphimine (**37**, norBNI) and binaltorphimine (**38** , BNI)[45]. Both compounds displayed exceptionally high κ-opioid receptor antagonist potency and selectivity[46, 47]. Related derivatives of the parent compound have been prepared to examine the function of the pyrrole moiety in conferring κ-selectivity at the opioid receptor[48]. The thiophene analogue (**40**) has a selectivity comparable with norBNI, while the pyran (**41**) is considerably less selective for the κ-site. The results suggest that the pyrrole moiety in norNBI serves primarily as spacer.



37 R=H (norBNI)
38 R-CH_3 (BNI)



39 (*meso*-norBNI)



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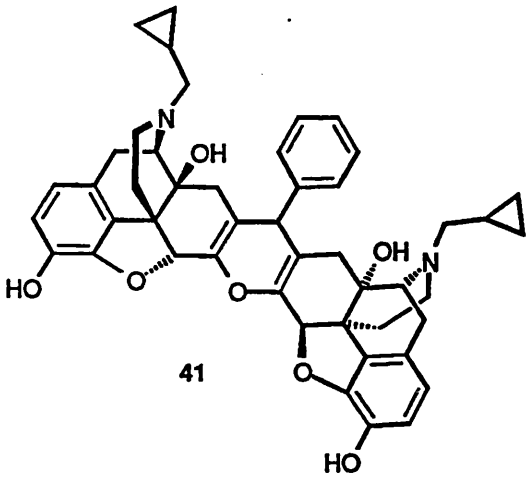

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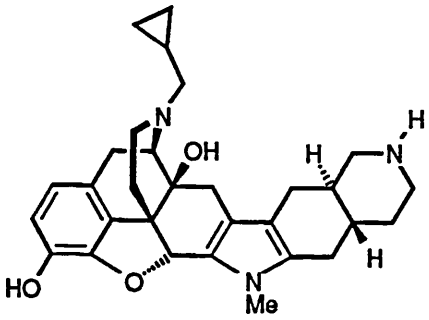
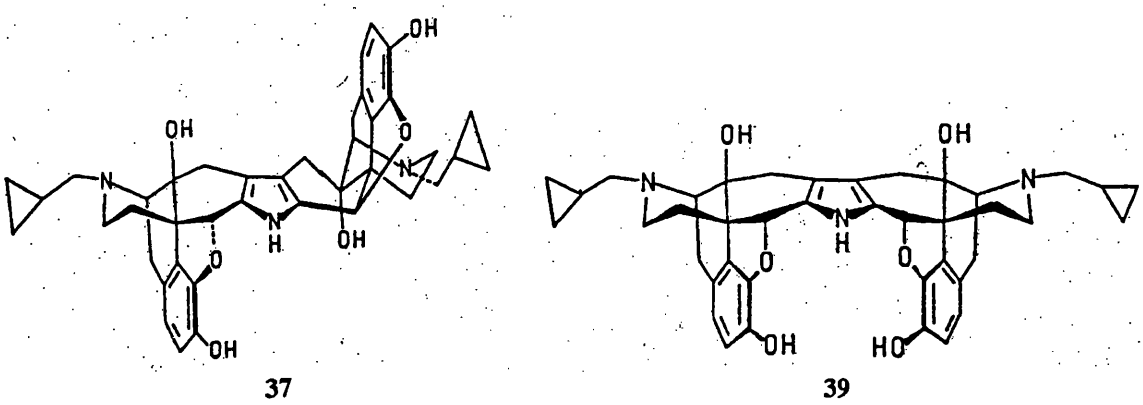


42

From structure activity studies[49, 50], it was revealed that norBNI (37) may not require a second pharmacophore for its high antagonist potency and selectivity. This theory was supported by the reported increase in potency of *meso*-norBNI (39), which contained the inactive (+)-naltrexone. The different geometry of the two molecules (**Figure 5**) suggests that κ-opioid antagonist selectivity cannot be ascribed to the bridging of two neighbouring opioid receptors and provides additional support that only one of the two antagonist pharmacophores of norNBI was required for κ-opioid receptor antagonist selectivity.



37 39

Figure 5 : Geometrical comparison between norBNI (**37**) and *meso*-norBNI (**39**)

From these results, Portoghese postulated that the (-)-naltrexone derived component of norBNI and its *meso* isomer bind to a recognition locus while the position of the basic nitrogen on the second pharmacophore serves as an Arg^7 mimic of the endogenous κ-selective opioid peptide dynorphin. The Arg^7 residue has been shown to be essential for κ-opioid activity[51]. The importance of the second nitrogen was illustrated by the simplified BNI congener **42**[52]. Compound **42** is less potent but twice as selective as norBNI at κ-sites which strongly suggests that the peripheral groups of **37** do not play a key role in the determining κ-selectivity.

1.8.2. Message-Address Concept

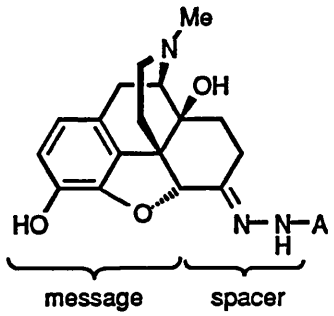
The message-address concept, proposed by Schwyer[53], was used to analyse the structure-activity relationships of various peptide hormones. In essence, peptide hormones which are sychnologically organised, contain a message sequence and an address sequence of amino acid residues, each being close to one another in the peptide chain. The message component is responsible for signal transduction at the receptor, while the address component provides additional binding affinity and is not essential to the transduction process. For a group of peptides associated with more than one receptor type the message component is very similar or invariant while the

address segment is variable and a determinant of selectivity for a particular type of receptor.

Chavkin and Goldstein[51] pointed out that the endogenous opioid peptides appear to conform to the message-address concept in that they contain a constant tetrapeptide sequence (Tyr-Gly-Gly-Phe) that can be viewed as the message and a variable sequence that can operate as an address in conferring selectivity. This address sequence is presumably complimentary to the receptor type that is unique for each opioid receptor site.

Another interpretation of the message-address concept as applied to opioid peptides, is that the tyrosine residue comprises the message component and the sequence commencing from Phe^4 constitutes the address, in this context Gly^2-Gly^3 serves as a spacer[54]. This alternate view is consistent with the well known structure activity relationships of non-peptide opioid ligands (e.g. morphine) that contain only one aromatic ring which presumably mimics the tyrosine residue.

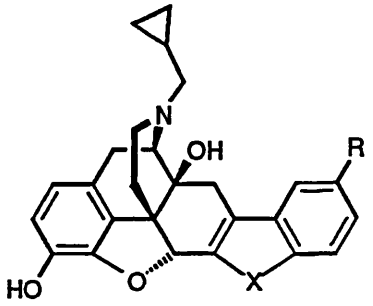
This concept was examined by Lipkowski and co-workers[55] who reported that a typical μ-selective ligand such as oxymorphone (**17**) can be transformed into a δ-selective ligand by attachment of an enkephalin dipeptide unit (Phe-Leu) through a hydrazone spacer to the C-6 position of the opiate (**Figure 6**). Similarly, a κ-selective ligand can be synthesised by attachment of a dynorphin related 'κ-address' (Phe-Leu-Arg-Arg-Ile-OMe). Although the message-address concept was originally proposed for endogenous agonists, the results suggested the feasibility of developing non-peptide δ-selective opioid antagonists by the attachment of an appropriate non-peptide moiety that would mimic a key recognition element in the δ-address.



A (address)	selectivity
Phe-Leu-OH	δ
Phe-Leu-Arg-Arg-Ile-OMe	κ

Figure 6

As with the bivalent ligands, the design of non-peptide δ-antagonists was explored using a naltrexone (**19**) as the 'message' component. The phenyl group of the Phe[4] residue of enkephalin was considered to be the key δ-receptor 'address' component. An important consideration in the design was the conformational restriction of this benzene moiety because a rigid address moiety was thought to confer greater δ-selectivity by precluding possible conformation adaptation of the ligand in the binding to other opioid receptor types. The first candidate to fulfil the above criteria possessed the indole system.

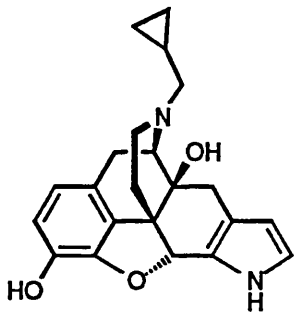


	X	R	
43	NH	H	naltrindole (NTI)
44	NH	F	
45	NH	F	
46	NH	Me	
47	NMe	H	
48	O	H	naltriben (NTB)

Indoles **43-47** were synthesised from naltrexone and the appropriate substituted phenylhydrazine under Fischer indole conditions[56]. In smooth muscle preparations, these indoles selectively antagonised δ-opioid agonists. The most potent member of the series is naltrindole (**43**, NTI). By way of comparison, the enkephalin analogue ICI174864 currently employed as a δ-antagonist possessed a potency of 1/530 that of NTI. In terms of δ-receptor binding, NTI has over a 1000 fold greater affinity than ICI174864[57]. The importance of the benzene moiety in conferring δ-

selectivity was shown by compounds **49** and **50**. The former, which contains the pyrrole moiety only, was found to be a μ-selective ligand while the reduced indole (**50**) is δ-selective but has considerably lower potency relative to NTI. Other heterocyclic analogues of NTI containing benzofuran (**48**), quinoxiline (**51**), and quinoline (**52**), and 6-aryl-naltrexone derivatives (**53** and **54**) were synthesised to examine the role of the spacer[58, 59]. Analogues **48** and **50-54** were all opioid antagonists and bind selectively to δ-receptors indicating that other heterocycles can serve as spacers. The 6-aryl derivatives, however, possessed considerably lower opioid receptor antagonist potencies which was considered to be due to the conformational mobility of the aryl group and its location in the molecule.

The role of conformation of the δ-address was explored further[60] with the benzylidene (**55**), 7α-benzyl (**56**), and epimeric anilino (**57** and **58**) compounds. All conformationally mobile analogues were shown to have relatively weak δ-opioid receptor antagonist potency as their aromatic groups are located in an area of space that is different from that of the more potent analogues.



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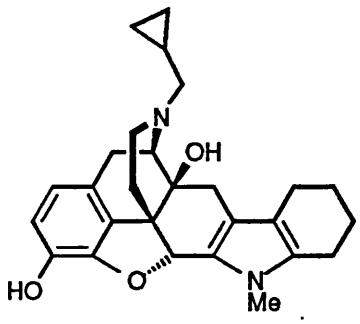

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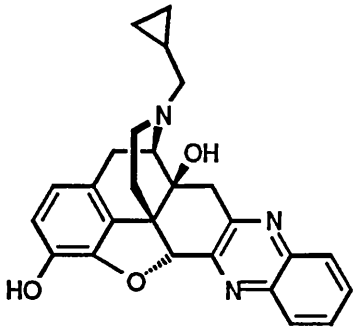

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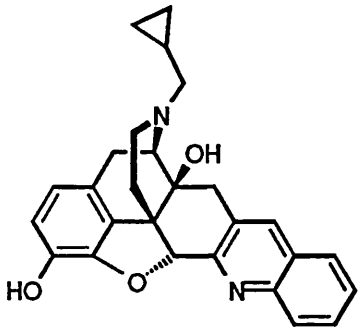

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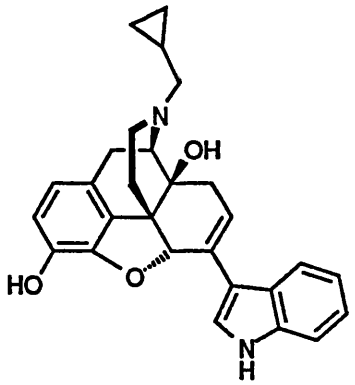

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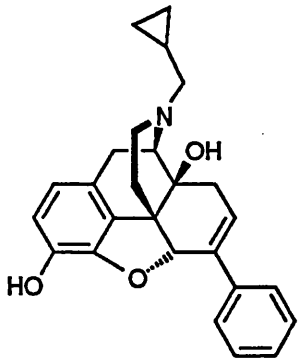

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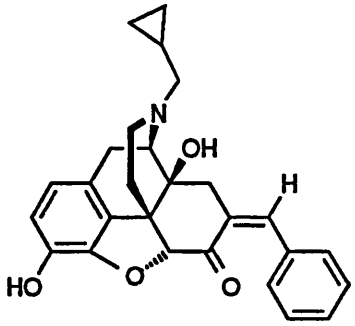

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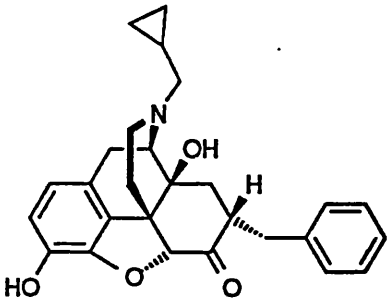

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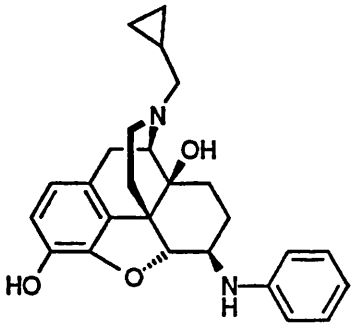

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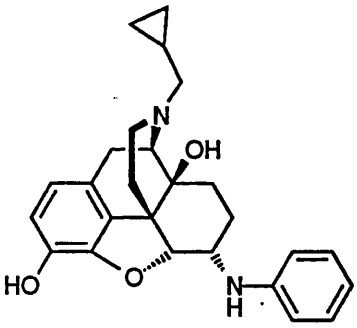
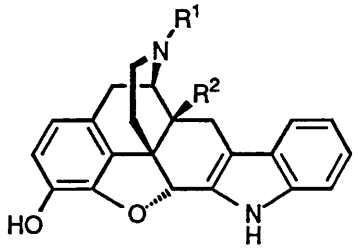


58

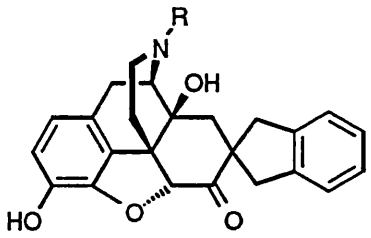
Attempts to transform NTI from a δ-antagonist to a δ-agonist by replacement of the cyclopropylmethyl with a methyl (**59**) and other *N*-substituted groups (**60-65**) were explored[61, 62]. As oxymorphone (**17**) is a potent μ-selective agonist, it was anticipated that oxymorphindole (**59**, OMI) might be a δ-selective agonist if the conformational requirements of δ-agonists and antagonists are similar. On the mouse *vas deferens* (MVD), OMI acted as a partial agonist (65% of maximum response), and

it was virtually inactive on the GPI. The fact that OMI was antagonised by NTI suggests that the agonist effect is mediated through the δ-receptor system. The partial δ-agonist character of OMI raised an possibility that the receptor bound conformations of agonists and antagonists differ. Morphindoles **60** and **61** were shown to be agonists but *in vivo* pharmacology found that compound **60** was not antagonised significantly by selective opioid antagonists, while that of phenethyl compound (**61**) is a relatively κ-selective agonist.

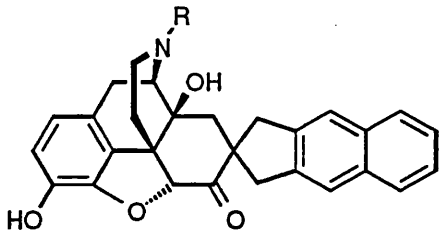


	R^1	R^2	
59	CH_3	OH	(OMI)
60	H	OH	
61	$CH_2CH_2C_6H_5$	OH	
62	H	H	
63	CH_3	H	
64	$CH_2CH_2C_6H_5$	H	
65	$CH_2CH{=}CHC_6H_5$	H	

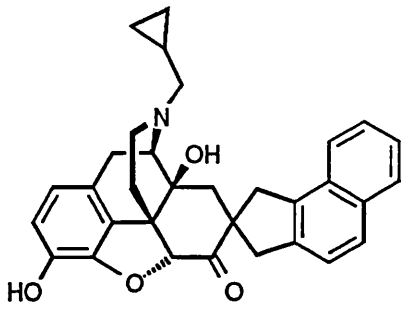
The retention of δ-antagonist activity by OMI prompted Portoghese to suggest that the conformation of the δ-address component in these compounds might preferentially stabilise an antagonist state of the δ-receptors in the CNS. This proposal led to the synthesis of spiroindanyloxymorphinone (**66**, SIOM) and spiroindanylnaltrexone (**67**, SINTX) where the benzyl moiety (address) of the indanyl substituent is rigidly held in the orthoganol position relative to ring C of the morphine skeleton[60, 63]. This position is considered to mimic the conformation of the Phe^4 phenyl group of [Tyr-D-Pen^2-Gly-Phe-D-Pen^5]enkephalin (DPDPE), a δ_1-agonist selective peptide. Pharmacological evaluation of the naltrexone derivative **67** showed it to be a potent δ-receptor antagonist while the *N*-methyl analogue **66** is apparently both a agonist and antagonist at the δ_1-receptor.



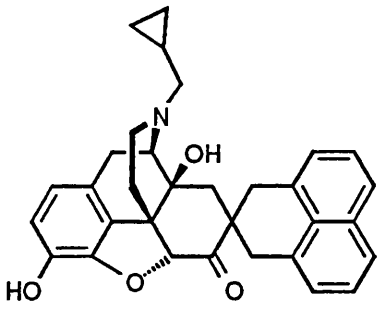
66 R = Me (SIOM)
67 R = CPM (SINTX)



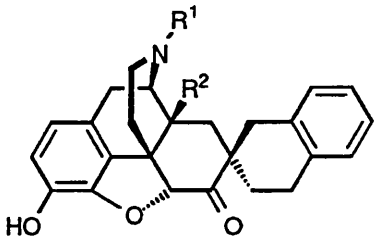
68 R = CPM
69 R = Me



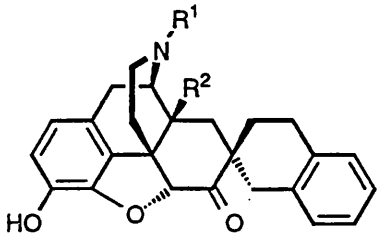
70



71



72 R^1 = CPM; R^2 = OH
73 R^1 = CH_3; R^2 = OH
74 R^1 = CH_3; R^2 = H



75 R^1 = CPM; R^2 = OH
76 R^1 = CH_3; R^2 = OH
77 R^1 = CH_3; R^2 = H

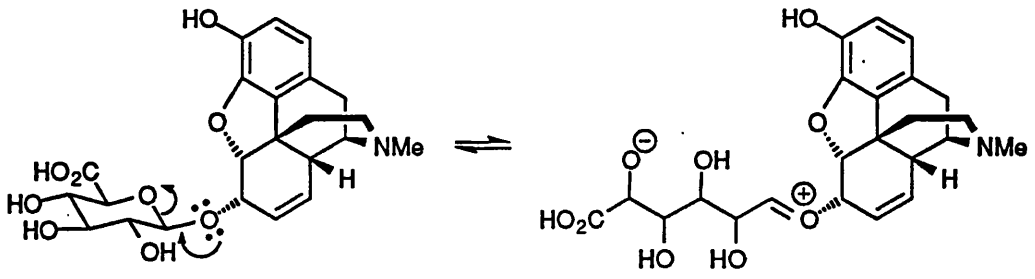
Further naltrexone, oxymorphone, and dihydromorphone derivatives in this series were synthesised which contained substituted spiroindanyl (**68** and **69**), benzospiroindanyl (**70**), spiroperinaphthyl (**71**), and spirobenzocyclohexyl (benzyl address is orientated differently in the 7α (**75-77**) and 7β (**72-74**) epimers) groups in an effort to explore structure-selectivity relationship of ligands that possess an orthogonal aromatic system relative to ring C of the morphinan[64, 65]. Although pharmacological results were far from conclusive, it was inferred that both coplanar and orthogonal conformations (relative to ring C of the opiate) of the aromatic address

moiety are capable of conferring δ-antagonist activity. However, δ_1 agonism appeared to be associated with an orthogonal-like conformation of the address. It also appears that the 14-hydroxy group of the opiate pharmacophore contributes significantly to the δ agonist activity.

1.9. Project Aims

1.9.1. CH_2 isosteric analogues of M6G

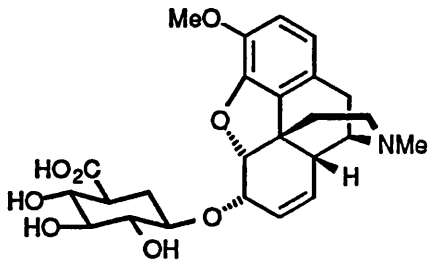
The ability of M6G, and to a lesser extent M3G, to penetrate the blood brain barrier has been attributed to the facility of these metabolites to display a high degree of lipophilicity over a wide pH range. Testa and co-workers have suggested that the glucuronides are able to behave as 'molecular chameleons' by varying their polarity depending on that of the medium[34]. Theoretical studies show that M6G exists predominantly, at physiological pH, in a 'folded' conformation with the sugar moiety eclipsing the morphine unit and is therefore able to mask a significant portion of its polar regions from the solvent. In contrast, the morphine and glucuronide moieties of the 'extended' conformer interact minimally through space and are maximally exposed to the solvent. The glucuronides therefore exist predominantly as extended, polar conformers in water and as folded, more lipophilic conformers in media of low polarity such as biological membranes.



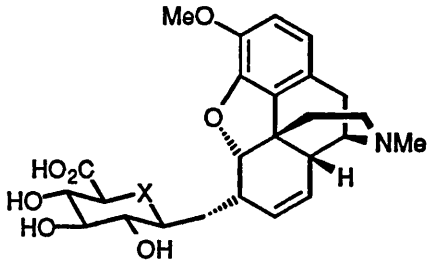
30 78

An alternative view offered by Lacy suggests that M6G (**30**) could exist in equilibrium with the open-chain (**78**) isomer[66]. This structure may have more freedom to expose or mask its polar groups than the closed-ring conformation and it is this which causes the variation in polarity and lipophilicity allowing a high level of blood transport with the ability to pass into biological membranes. To explore this possibility, compounds **79**, **80** and **81** were proposed where the oxygen atom in the

glucuronide moiety or in the sugar-morphine linkage or both have been replaced with a CH_2 isosteric unit respectively. All three compounds are therefore unable to exist in the open-chain form but may equilibrate between the extended and folded forms described by Testa *et al.* It is anticipated that these targets may shed light on the important structural-activity relationships of M6G and may themselves prove to be effective analgesics.



79



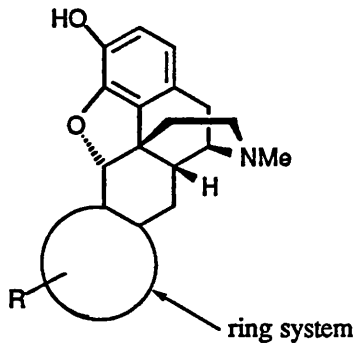
80 X=O
81 X=CH_2

Attempts by Lacy to synthesise the first of the CH_2 isosteric targets, pseudosugar derivative **79**, proved unsuccessful[66]. Several procedures were examined to effect the coupling between morphine or codeine with a pseudosugar equivalent, but difficulties encountered in forming this ether linkage were parallel to those observed in the various attempted syntheses of M6G itself. In a continuation of this work, we examined possible routes to the second and third of Lacys' targets, *i.e.* compounds **80** and **81**.

1.9.2. C-6,7-Ring Fused Morphines

The fact that M6G is a more potent analgesic than morphine suggests that there may be a cavity within the opioid receptor which specifically accommodates the sugar moiety to increase activity. We therefore considered that if the steric bulk of ring C could be increased so that the groups attached 'projected' into the same area of

the receptor site as the sugar residue (**Figure 7**), then these compounds should prove to be pharmacologically active.



R = polar or lipophilic group

Figure 7

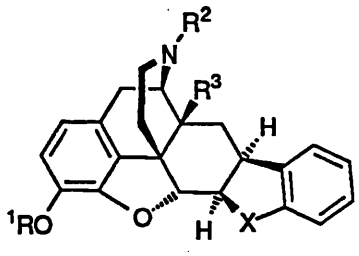
When considering suitable substituents to provide the steric bulk required at ring C, we thought that if the group could instil some extra rigidity to the system then activity may further be enhanced. Increased rigidity of ring C, as seen in Diels-Alder adducts of thebaine, assists in increasing opioid activity but it is not the sole criterion for high potency, *i.e.* variation of the *N*-substituent, changes in the conformation of the ring system, and the nature of the substituents also bring about dramatic changes in biological activity. If an additional ring system could be fused onto ring C of morphine, then various other polar or lipophilic groups attached to this ring could be included later providing a probe into receptor site requirements and analgesic activity.

1.9.3. Naltrindole Conjugates

Utilisation of the message-address concept has shown that the conformation of the aromatic address moiety plays an important role in conferring selectivity at an opioid receptor. Studies thus far have centred on the synthesis of compounds where the benzene address moiety has been held rigidly in a co-planar or orthogonal plane with respect to ring C of the morphinan skeleton. These two positions are reported to mimic the orientations of the Phe^4 residue of enkephalin and DPDPE respectively and

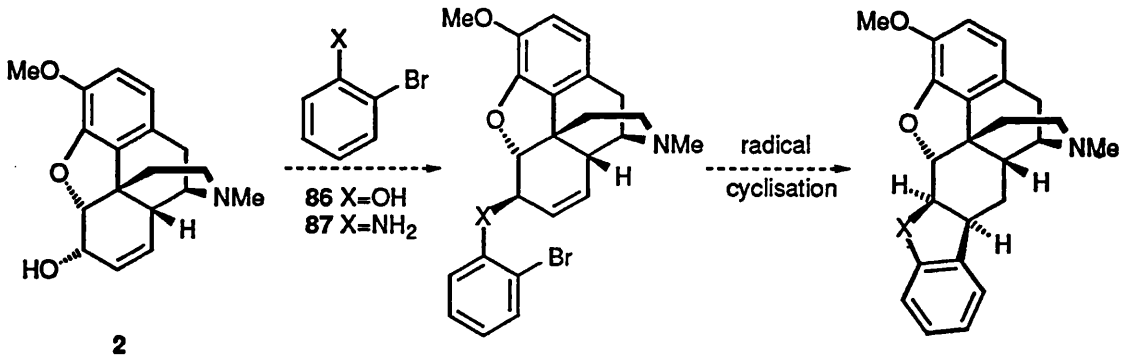
have led to the successful development of potent, non-peptide, opioids ligands such as NTI (**43**) and SIOM (**66**)which are δ-selective.

As conformational requirements of the so called address moiety play an important role in selectivity, we considered it of interest to study compounds of the type **82-85**. We envisage that saturation of the 6,7-double bond of compounds like NTI and its conjugates would lead to structures in which the benzene moiety is held in a position 90° to the plane of ring C of the morphinan.



82 X=O; R^1=R^2=CH_3; R^3=H
83 X=NH; R^1=R^2=CH_3; R^3=H
84 X=O; R^1=H; R^2=CPM; R^3=OH
85 X=NH; R^1=H; R^2=CPM; R^3=OH

Our initial targets would be compounds **82** and **83**. The proposed two step synthetic route is shown in **Scheme 1**. Mitsunobu reaction of codeine (**2**) with the appropriately substituted 2-bromobenzene would generate intermediates **88** and **89** respectively which, under radical cyclisation conditions, would be expected to undergo a 5-*exo*-trig ring closure to the desired compounds.



2

88 X=O
89 X=NH

82 X=O
83 X=NH

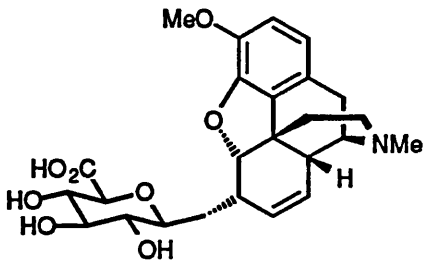
Scheme 1

If the pathway is successful we hoped to extend the study to the synthesis of the naltrexone type derivatives **84** and **85**.

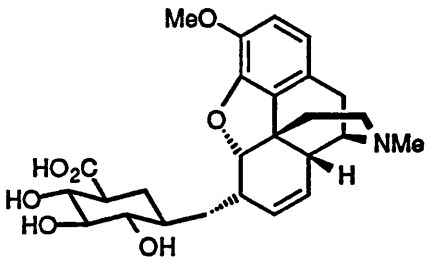
CHAPTER 2

RESULTS AND DISCUSSION

2.1. CH_2 Isosteric analogues of M6G



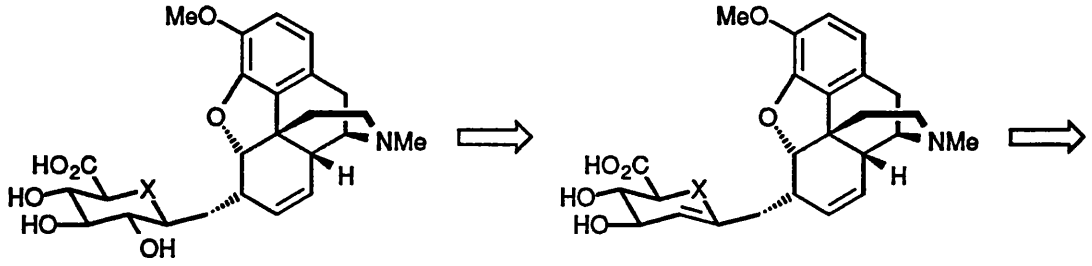
80



81

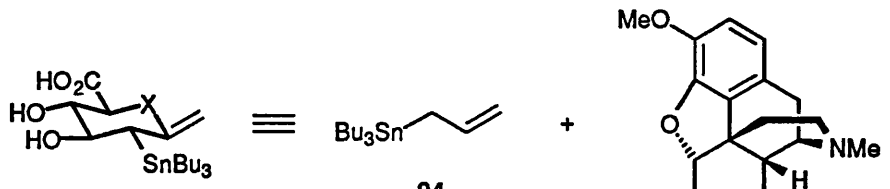
The key step in the syntheses of Lacys' second and third CH_2 isosteric targets, compounds **80** and **81**, involves the formation of the C-C link between the aglycon, a codeine derivative and a suitable glucuronide moiety. Interest, within our group, in radical chemistry led retrosynthetically to two precursors, 6-bromocodide (**95**) and sugar derivative **92** or **93**.

As we were primarily interested in the coupling methodology between the two units and bearing in mind the often lengthy multi-step route to sugar compounds, we chose allyltri-*n*-butyltin (**94**) as a simple model compound for both carbohydrate precursors **92** and **93** (**Scheme 2**).



80 X=O
81 X=CH_2

90 X=O
91 X=CH_2



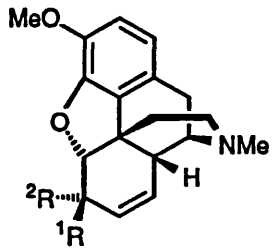
92 X=O
93 X=CH_2

94

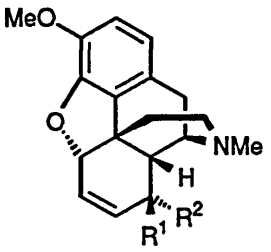
95

Scheme 2

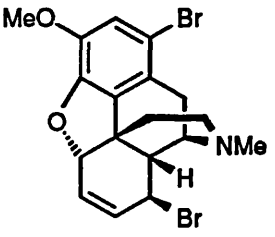
An extensive literature search revealed several references describing the bromination of codeine. When gently boiled with hydrobromic acid, codeine affords 'bromocodide' although yields are very low and the product difficult to isolate in the pure state[67]. Treatment with thionyl bromide also generates the bromocodide[68]. The method is nevertheless sensitive to excess thionyl bromide and bromination of the aromatic nucleus to give the dibromo compound, 1,8β-dibromocodide (**99**) can result. The latter compound has also been obtained by Lacy using phosphorus pentabromide[66].



96β ^{1}R=allyl; ^{2}R=H
96α ^{1}R=H; ^{2}R=allyl
95β ^{1}R=Br; ^{2}R=H
95α ^{1}R=H; ^{2}R=Br



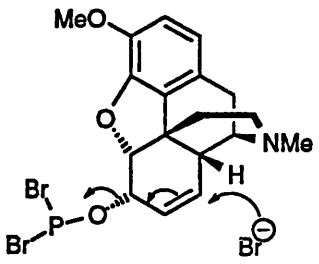
97β ^{1}R=allyl; ^{2}R=H
97α ^{1}R=H; ^{2}R=allyl
98β ^{1}R=Br; ^{2}R=H
98α ^{1}R=H; ^{2}R=Br



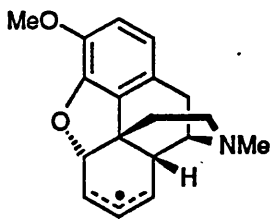
99

Early work by Schryver and Lees utilised phosphorus tribromide as the bromination agent[69]. However, these workers could only speculate as to the identity of the bromo compound they had actually synthesised due to the lack of physical evidence available at this early date. Structural studies by Stork[70] and later Jacobsen[71] confirmed that the 'bromocodide' isolated by Schryver and other workers cited above, was in fact 8β-bromocodide (**98β**). The formation of the 8β-bromocodide suggests that nucleophilic attack by bromide ion on the organophosphorus intermediate **100** takes place preferentially at the 8-position from the sterically least hindered β-face with allylic rearrangement (S_N2') to the major product. The sterically retarded 6-position is not accessible to the usual back-side attack (S_N2) and therefore does not takes place. S_N1 Substitution has not been

considered by previous authors, but cannot be ruled out even though only one product, 8β-bromocodide, has been isolated.



100



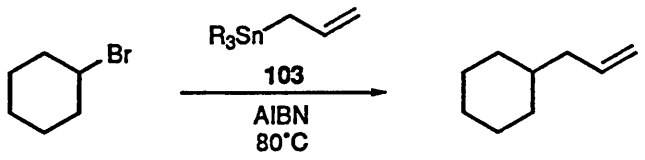
101

Although we had initially envisaged coupling the 6-bromocodide (**95**) rather than the 8β-bromocodide (**98β**) with allyltri-*n*-butyltin, further consideration with respect to the allyl system in the morphinoid meant that the position of the bromine in bromocodide is irrelevant since dehalogenation in the next step would give rise to the same allyl radical (**101**). Our principle concern for the next step however, was the regio- and stereoselectivity of the radical coupling between bromo compound and allyltri-*n*-butyltin. The radical species (**101**) generated from debromination of 8β-bromocodide could undergo coupling at either the 6- or the 8- position and, in addition, coupling from the α- or β-face is likely *i.e.* four compounds **96α**, **96β**, **97α** and **97β** are possible although it was hoped that there would be some degree of selectivity.

In the first step of the synthesis, we found that bromination of codeine (**2**) with phosphorus tribromide actually gave rise to a mixture of two regioisomers, the expected 8β-bromocodide (**98β**) and also 6β-bromocodide (**95β**) which were difficult to separate by column chromatography. The overall yield was 83% with an isomer ratio of 3:1 (by ^{1}H-NMR) in favour of the 8β-compound. This is in contrast to the result obtained by Stork who reported that the same reaction gave an isolated yield of 55% of the 8β-bromocodide only[70].

The allylation of halogenated substrates via a radical mechanism using allyl stannanes was first introduced by Keck in 1982 and has subsequently found use in a

large variety of syntheses[72]. The general process is summarised below in **Scheme 3** and the reaction is reported to be tolerant of a wide range of functional groups.

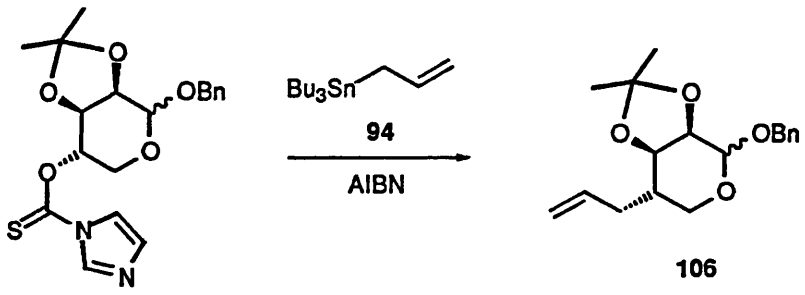


102 104

Scheme 3

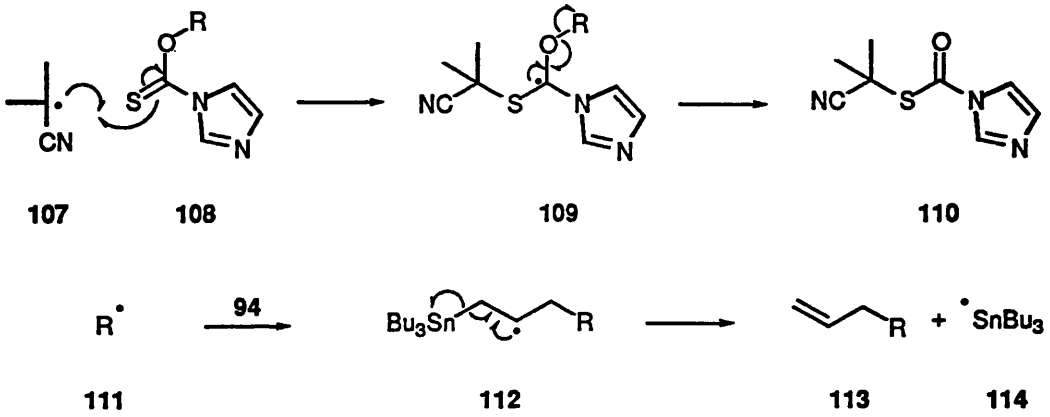
Our first attempts to effect the coupling between 'bromocodide' and allyltri-*n*-butyltin used a mixture of 6β-bromocodide and 8β-bromocodide, without separation. Addition of 0.15 equivalents of AIBN, as radical initiator, to the reaction mixture gave no reaction after 2 hours. Addition of further quantities of AIBN however, gave rise to a reaction yielding at least six different compounds (by TLC), of which unreacted starting material (isolated) was the major component. Complete separation of the new minor compounds from the reaction mixture by column chromatography proved difficult due to their similar R_f values. Analysis of the separated fractions by ^{1}H-NMR spectroscopy did not reveal any additional proton signals in the chemical shift region 5.5-6.5ppm which would be synonymous with an allylic side chain. The absence of the target compound **96** from the mixture was supported by mass spectrometry data which showed the presence of unreacted starting material (M^+ = 362) but did not contain a mass ion peak at *m/z* 323 corresponding to compound **96.**

Separation of the regioisomers by column chromatography and attempted coupling of pure 8β-bromocodide (**98**β) with allyltri-*n*-butyltin again failed. Reactions carried out at the boiling temperature of toluene showed only rapid decomposition of the 8β-bromocodide to 7 components, at least, which were not identified.



105 106

Scheme 4

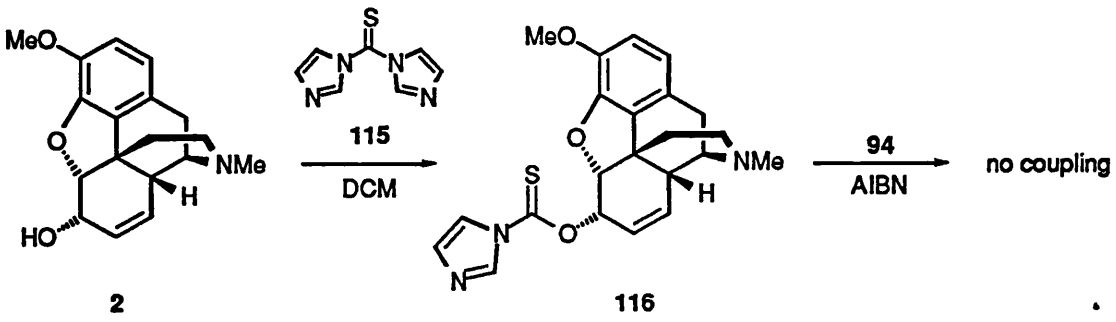


107 108 109 110

111 112 113 114

Scheme 5

Reports also by Keck and Yates[72] that thiocarbonylimidazole derivative **105** underwent allylation to give pentose **106** as a single product (**Scheme 4**) prompted us to investigate this alternative coupling procedure. The reaction is assumed to proceed through the mechanism shown in **Scheme 5**. Attack by radical initiator **107**, obtained from fission of AIBN, on the thio group followed by fragmentation of **109** affords the radical **111**. Subsequent reaction of R• with allyltri-*n*-butyltin generates the β-stannyl radical **112** which undergoes fragmentation by β-bond cleavage to afford the product **113** and the chain propagating tri-*n*-butyltin radical **114**.

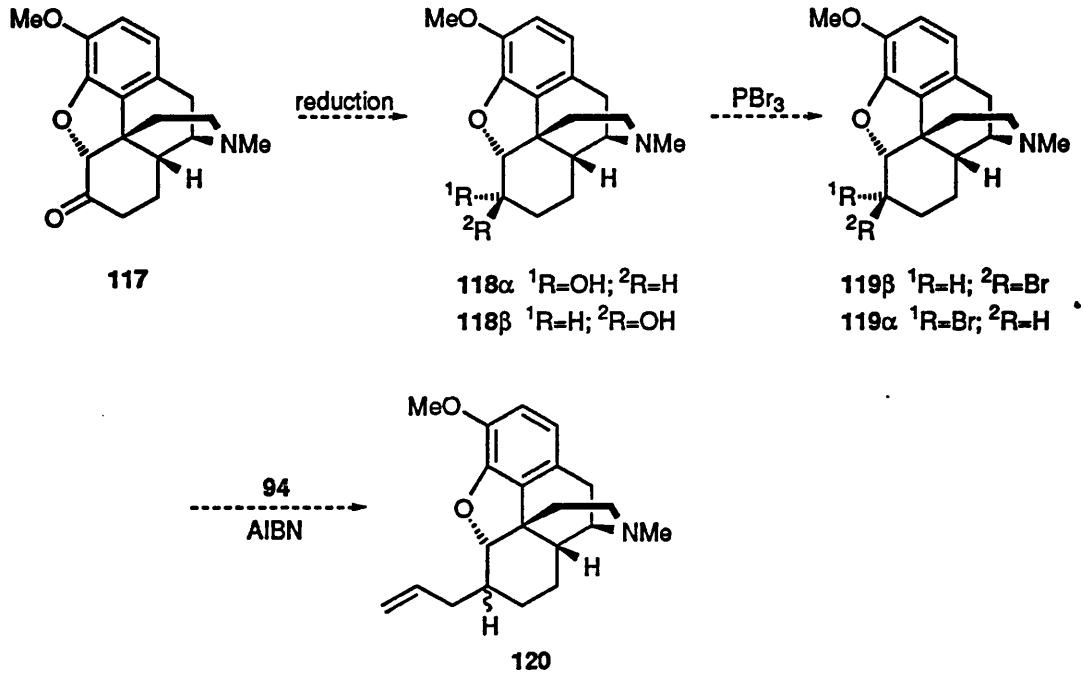


Scheme 6

6α-O-(Thiocarbonylimidazole)codeine (**116**) was prepared in 42% yield from codeine under essentially neutral conditions using *N,N'*-thiocarbonyldiimidazole (**115**), according to the procedure of Barton[73]. However, attempted radical mediated allylation of **116** again yielded no clean coupled product, but instead gave very complex mixtures.

The failure of bromocodide and the thiocarbonylimidazole derivative to undergo allylation and the isolation of numerous products from the reaction mixtures, albeit unidentified, led us to believe that the morphinan radical (**101**) may undergo rapid decomposition before reaction with allyltri-*n*-butyltin can take place. This process may be exacerbated by the presence of the 7,8-double bond in 8β-bromocodide which extends the opportunity for intramolecular reactions to occur, perhaps leading to ring-opening of the reduced isoquinoline ring.

In order to test this theory, we decided to investigate the same coupling reaction using 6-bromodihydrocodide (**119**) in which the endocyclic 7,8-double bond is absent. The overall route to target **120** is shown below in **Scheme 7.**



117

118α ^{1}R=OH; ^{2}R=H
118β ^{1}R=H; ^{2}R=OH

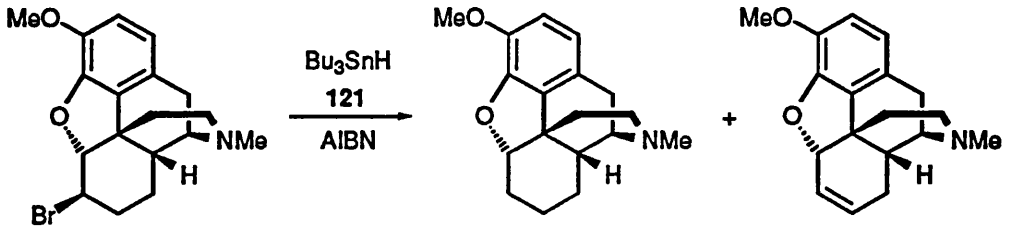
119β ^{1}R=H; ^{2}R=Br
119α ^{1}R=Br; ^{2}R=H

120

Scheme 7

Initially, reduction of dihydrocodeinone (**117**) was attempted with sodium borohydride as this reagent had previously been used by Gates in the stereoselective conversion of codeinone to codeine[74]. Although the reduction proceeded in good overall yield (94%), TLC analysis of the reaction mixture showed the presence of two compounds, presumably the diastereomeric alcohols, which were difficult to separate by column chromatography. Although we recognised that it was unnecessary to control stereochemistry in this reduction, out of interest, the formation of two components prompted us to evaluate more sterically hindered reducing agents such as diisobutylaluminium hydride[75] and K-Selectride[76] for the transformation. Both reagents gave a clean conversion to a single alcohol (by TLC) in isolated yields of 75% and 68% respectively. Molecular models suggest that attack by hydride ion is more likely to occur from the least hindered β-face to afford the 6α-alcohol (**118α**). A difference nOe study confirmed this hypothesis whereby signal irradiation at 4.04ppm (assigned H-6β) gave signal enhancements of 11.4, 5.7, and 2.1% for the assigned protons H-5, H-7α, and H-7β respectively.

Bromination of **118α** using phosphorus tribromide gave a 52% yield of the 6β-bromodihydrocodide (**119β**). A separate attempt to brominate **118α** with *N*-bromosuccinimide[77] was not successful and only starting material was recovered. Reaction of **119β** with allyltri-*n*-butyltin under standard conditions was again unsuccessful. The products which formed were unseparable by column chromatography and analysis of the mixtures by ^{1}H-NMR spectroscopy did not show any proton signals in the allylic region of the spectrum.



119β **122** **123**

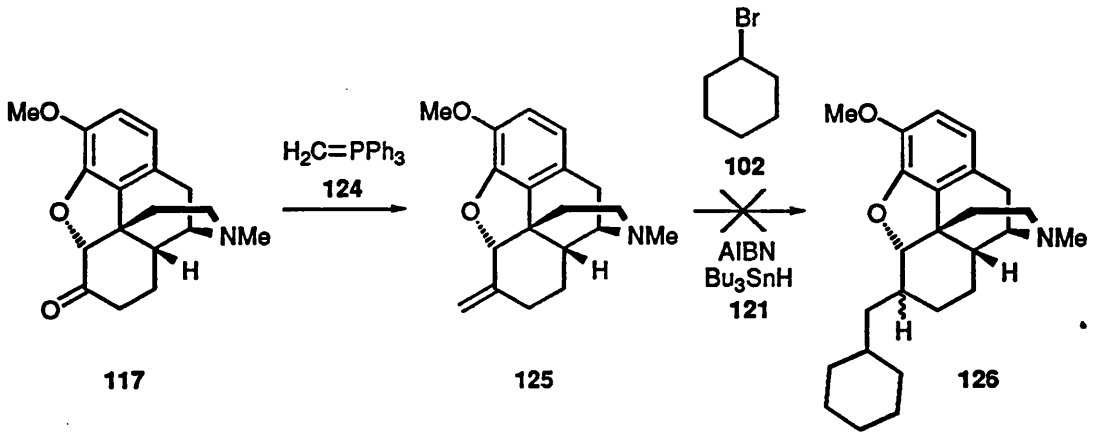
Scheme 8

The difficulties encountered in forming the C-C bond between morphinoid and allyltri-*n*-butyltin led us to examine some basic chemistry in this area. For example, we wished to know if dehalogenation of 6β-bromodihydrocodide (**119β**) with tri-*n*-butyltin hydride was a facile reaction. The replacement of halogen with hydride serving primarily to determine the efficiency of the radical reaction. It was hoped that this reduction would lead to the known compound dihydrodeoxycodeine D (**122**) in good yield.

Reaction of 6β-bromodihydrocodide with tri-*n*-butyltin hydride (**Scheme 8**) however gave rise to a 1:1 mixture of two compounds which were later identified as the desired compound **122** and deoxycodeine C (**123**). The result showed that the initially formed morphinyl radical is relatively unreactive to 'external' donors, even the 'simple' reagent tri-*n*-butyltin hydride prefers instead to eliminate a hydrogen atom. This did not bode well for coupling reactions with allyl radicals or their

equivalents. We now moved away from morphinyl radicals and turned our attention to the addition of radicals to methylenylmorphines.

Pioneering work by Giese highlighting the formation of carbon-carbon bonds by addition of free radicals to alkenes[78] led us to examine a further possible route to compound **126**, a simplified equivalent to target **81**. Reacting 6-(methylidenyl)dihydrodeoxycodeine (**125**), prepared from a Wittig reaction between dihydrocodeinone (**117**) and methylenetriphenylphosphorane (**124**)[79], with cyclohexylbromide in the presence tri-*n*-butyltin hydride (**Scheme 9**) however gave no reaction and an almost quantitative amount of starting material was recovered from the product mixture.



Scheme 9

Simple molecular orbital theory states that the energy differences between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of the reacting species are decisive in determining the rate of a reaction. The smaller the energy difference between these frontier orbitals, the greater the stabilising effect when the reactants approach one another. The frontier orbital of a free radical is the SOMO (single occupied molecular orbital) and this orbital will interact with both LUMO and HOMO of the alkene.

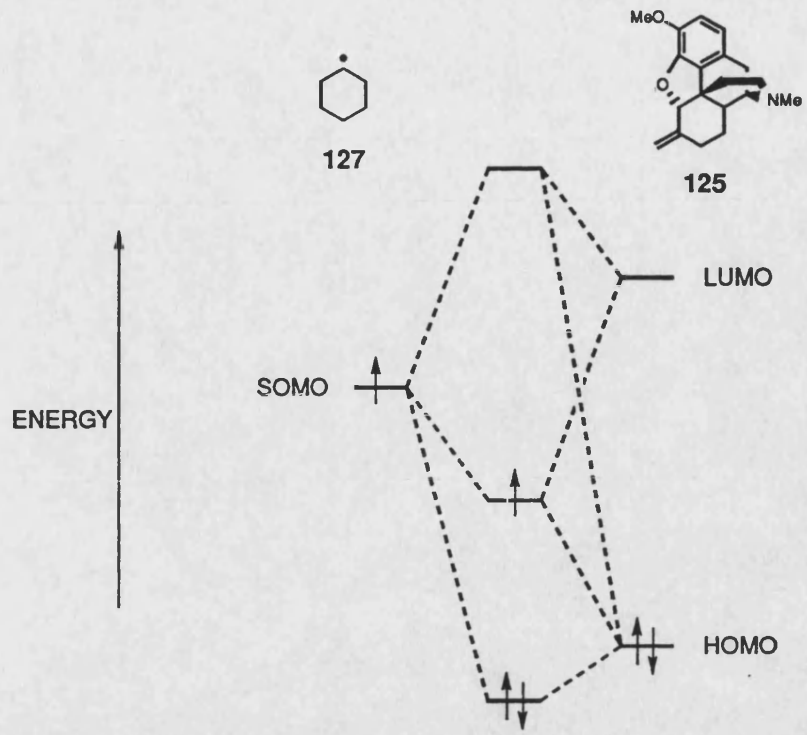


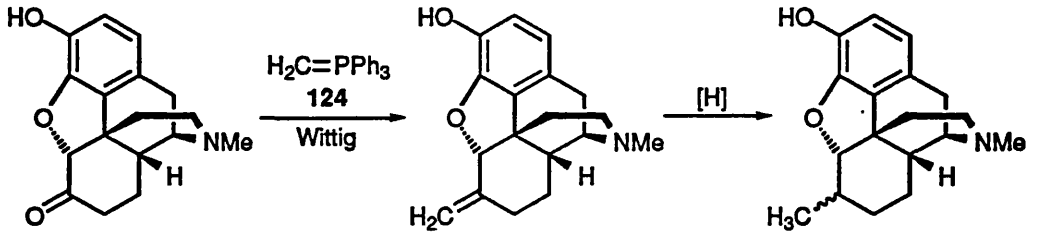
Figure 8

For nucleophilic radicals containing electron donating groups, the energy of the SOMO will increase and so alkyl radicals, such as cyclohexyl (**127**), with their high energy SOMO will interact with the LUMO of the alkene (**Figure 8**). The incorporation of electron-withdrawing substituents into the alkene lowers the energy of the LUMO and as a consequence the SOMO-LUMO energy difference decreases, and the rate of free radical addition increases. However, in our case the opposite is true. Thus, a tentative explanation for the failure of our reaction is that the morphinene is insufficiently electron poor to decrease the energy of the LUMO enough. As a result there is only a weak SOMO-LUMO interaction which in turn disfavours the reaction between cyclohexyl radical and morphinene.

In view of the unsuccessful results obtained via the radical pathway in forming carbon-carbon bonds we decided to abandon this route and explore a different synthetic strategy.

2.2 Wittig Chemistry

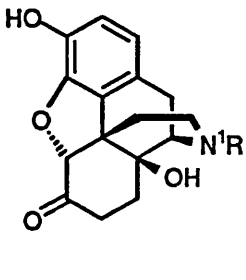
The Wittig reaction[80], since its introduction in 1953, has found little application in the field of morphine chemistry. Chadha and Rapoport[79] first reported its use in the preparation of 6-(methyl)dihydrodeoxymorphine (**130**) by reduction of 6-(methylidenyl)dihydrodeoxymorphine (**129**) although the stereochemistry at C-6 was unknown (**Scheme 10**). Indeed, this procedure works well and was utilised by us to prepare, in high yield, compound **125** for use in an attempted intermolecular radical coupling reaction (*vide supra*).



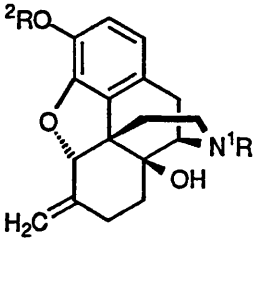
128 **129** **130**

Scheme 10

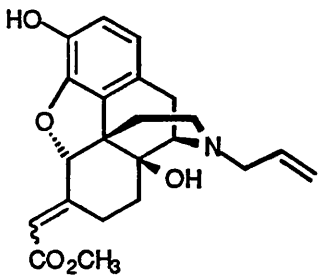
Hahn and Fishman have also described the synthesis of several novel 6-methylene narcotic antagonists (**131-134**) based on naloxone (**18**) and naltrexone (**19**) using the appropriate ylides[81]. This time these compounds were not reduced to the alkyl analogues.



18 ^{1}R=allyl
19 ^{1}R=H_2C—

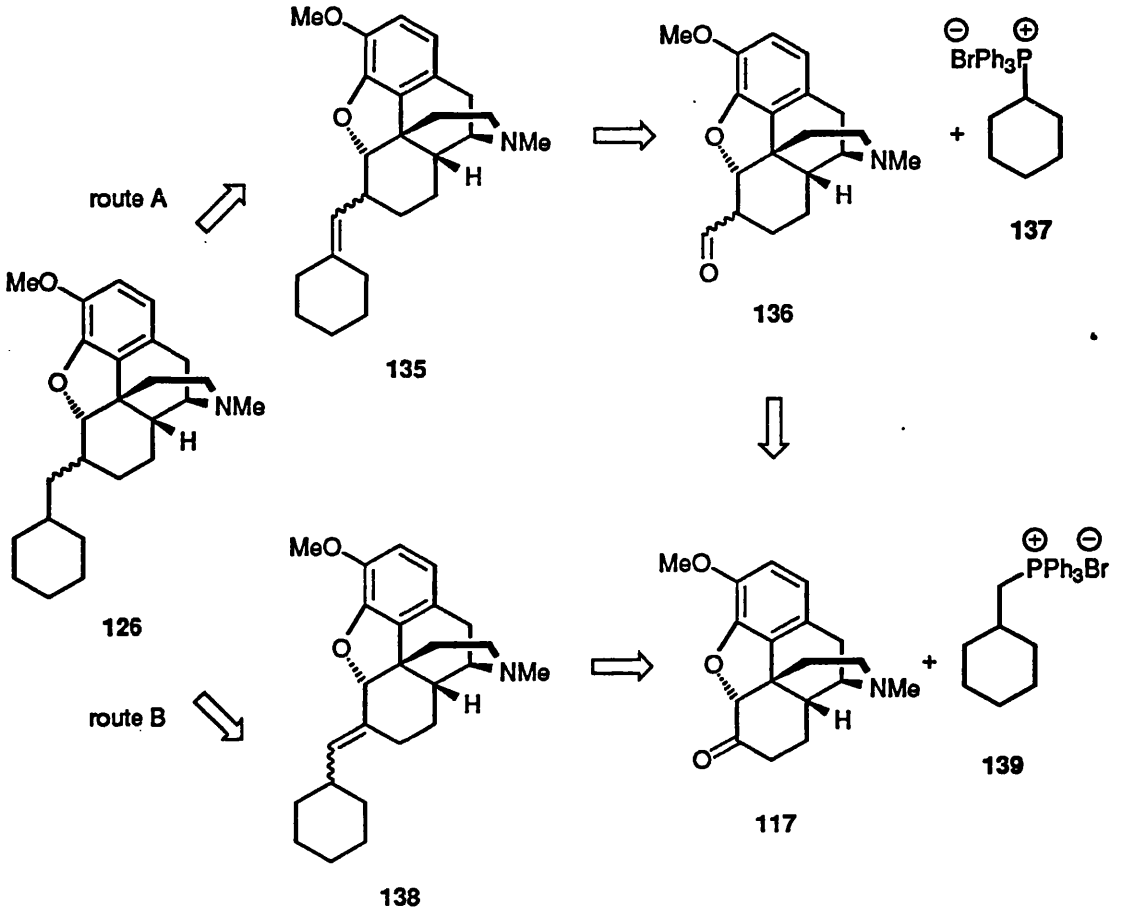


131 ^{1}R=allyl, ^{2}R=Ac
132 ^{1}R=CPM, ^{2}R=Ac
133 ^{1}R=CPM, ^{2}R=O_2CCH=CHPh



134

If target **81** in its simplest form *i.e.* compound **126** is considered, then one of our interests in the Wittig methodology stems from the realisation that the carbon-carbon linkage between 4,5-epoxymorphinan and cyclohexyl group (**Scheme 11**) could be derived from the double bond reduction of either alkene **135** or **138.**



Scheme 11

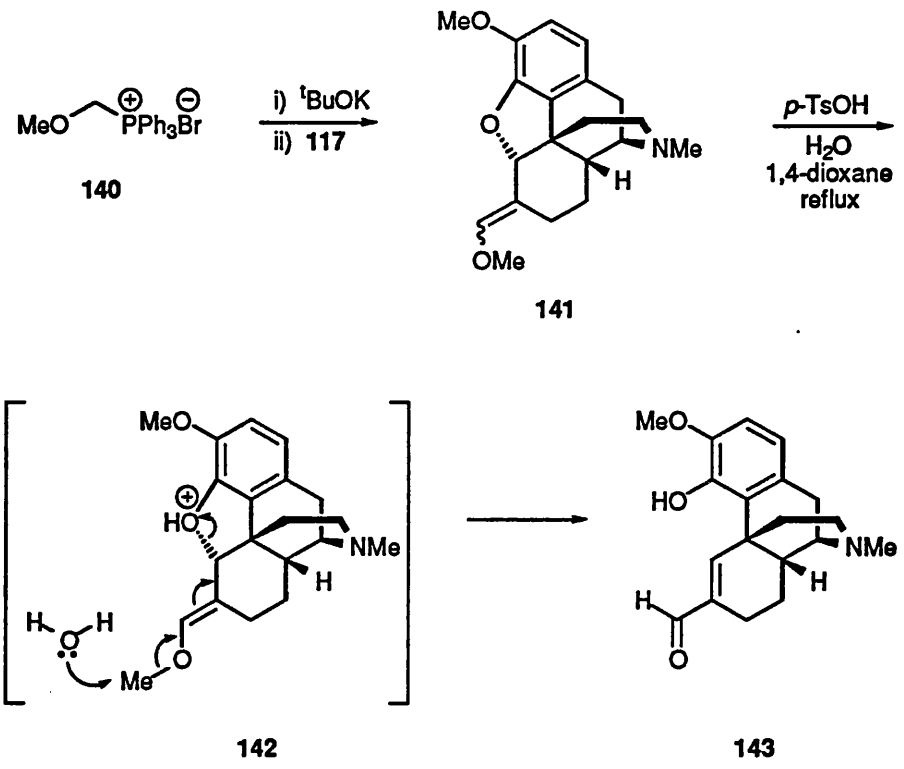
With this in mind, we envisaged two potentially viable routes to compound **126.** The first, route A, involves a double Wittig transformation, one to form the intermediate higher aldehyde **136** from dihydrocodeinone (**117**) whilst the second makes use of cyclohexyl triphenylphosphorane (**137**) to generate alkene **135.** This route was of particular interest for two reasons i) chain extension at the C-6 position by one carbon unit would perhaps facilitate reactivity at this position due to reduced steric encumbrance (compared with direct reaction at the 6-position) and ii) the

carbonyl functionality provides an excellent handle to further elaborate the morphine skeleton.

The second potential route involves direct reaction of **117** with cyclohexylmethyl triphenylphosphorane (**139**) (one extra carbon in the side chain) to yield **138**. Subsequent reduction of **135** or **138** would lead to target **126**. A further intriguing question for us was to ascertain which stereoisomer would be formed after reduction of compounds **135** and **138**.

Route A

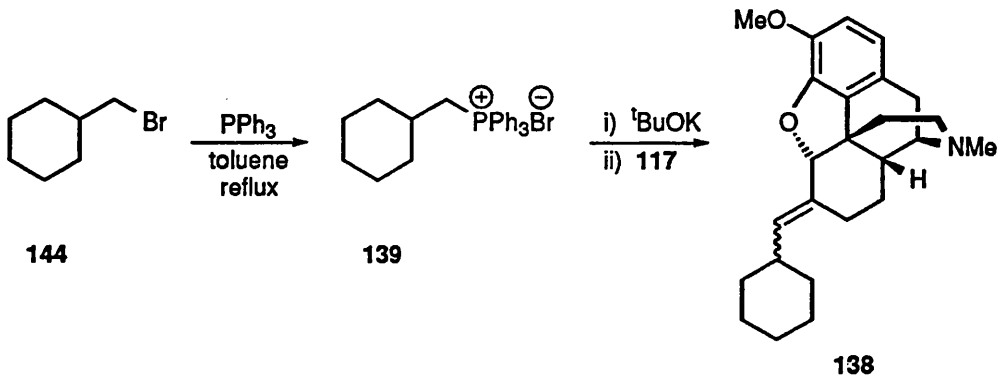
Reaction of methoxymethyltriphenylphosphonium bromide (**140**) with dihydrocodeinone (**117**) gave the intermediate enol ether **141** as an inseparable mixture of configurational isomers in the ratio 2.5:1, the higher ratio presumably in favour of the *E*-isomer[82]. However, attempted hydrolysis of this intermediate to the desired aldehyde **136** using *p*-toluene sulphonic acid proved unsuccessful giving rise to a new compound, the phenol **143** doubtlessly via intermediate **142** (**Scheme 12**). As acid conditions are required for hydrolysis of enol ethers and bearing in mind that the ether bridge in morphine analogues are susceptible to such ring opening under acidic conditions we decided that this route was not plausible and therefore turned our attention to route B.



Scheme 12

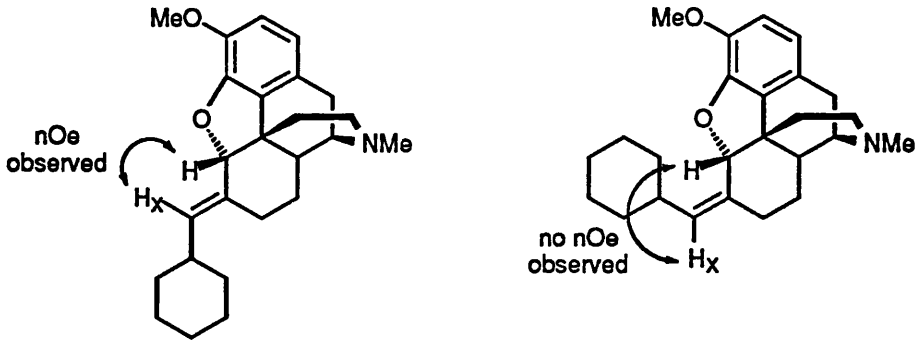
Route B

In the second route, cyclohexylmethyl triphenylphosphonium bromide (**139**), generated by boiling cyclohexylmethylbromide (**144**) and triphenylphosphine in toluene[83], was reacted with dihydrocodeinone (**117**) under standard Wittig conditions (**Scheme 13**). The reaction gave rise to **138** as a partially separable 1:1 mixture of *E*:*Z* isomers in 91% total yield.



Scheme 13

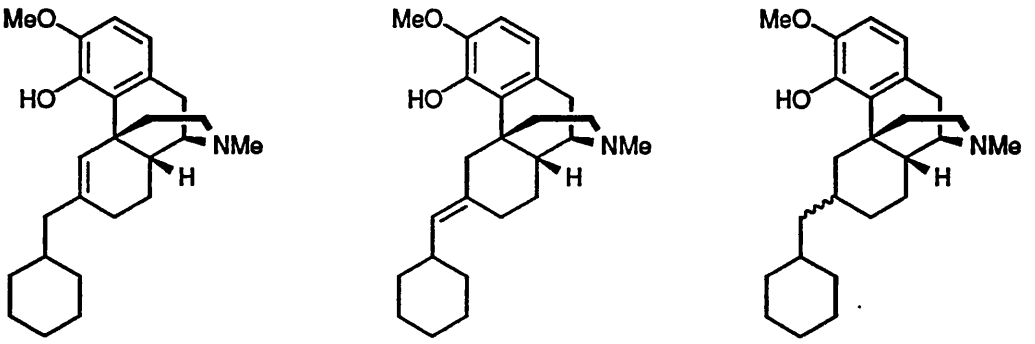
Examination of molecular models showed that a distinction between the geometrical isomers of **138** could be made through a consideration of proton H-5 and vinylic proton H_X (**Figure 9**). Thus, a nOe between these two protons should be observable in the ***E*-138** isomer but absent in the ***Z*-138** isomer. Indeed, this postulate was confirmed through an extended 2D nOe correlated spectroscopy experiment.



***E*-138** ***Z*-138**

Figure 9

In the next step, hydrogenation of **138** using palladium metal on charcoal at room temperature and atmospheric pressure proved unsuccessful. No reaction was observed (TLC) even when left over five days. Hydrogenation under more forcing conditions of higher pressure (45 atm) at room temperature and later increased temperature (50°C) also failed to induce any reaction. Acid promoted catalysis again at room temperature and atmospheric pressure returned mainly starting material but also a small quantity of the morphinene **145**.



145 **146** **147**

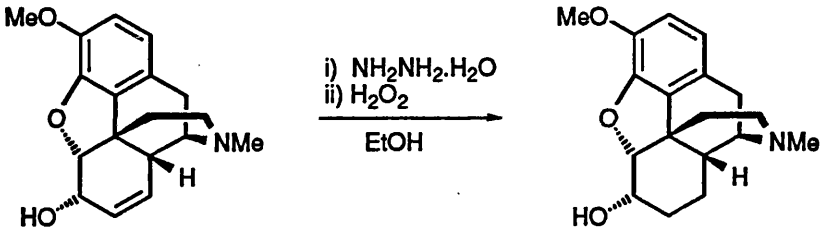
When *N,N*-dimethylformamide was used as reaction solvent instead of absolute ethanol, morphinene **145** was again isolated in 65% yield and also 8% of compound **146.** The results from catalytic hydrogenation of **138** are summarised in **Table 2.**

			isolated yield (%)			
conditions	catalyst	solvent	**138**	**126**	**145**	**146**
1atm, rt, 5 days.	Pd/C	EtOH	100	0	0	0
1atm, rt, HCl, 3 hr	Pd/C	EtOH	80	0	14	0
45atm, rt, 24 hr	Pd/C	EtOH	100	0	0	0
45atm, 50°C, 21 hr	Pd/C	EtOH	100	0	0	0
40atm, rt, 18 hr	Pd/C	DMF	0	0	65	8

Table 2

Due to the lack of success encountered during catalytic hydrogenation which we assumed to be a consequence of the inaccessibility of the catalyst surface to the sterically crowded trisubstituted double bond, we turned our attention to chemical methods of reduction. Triethylsilane and trifluroacetic acid have commonly been employed in the reduction of double bonds[84]. However, in our case the frailty of compound **138** to an acidic environment again prevailed, the ether bridge being cleaved to give morphinene **145** and compound **147.**

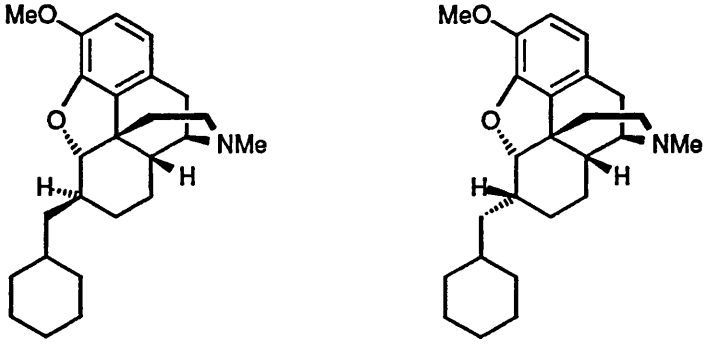
Our next step was to use the diimide as reductant[85]. As diimide is unstable we chose to generate the species *in situ* by oxidation of hydrazine hydrate using hydrogen peroxide[86]. Initially we attempted a trial reduction of codeine (2) simply to determine the efficiency of the process. The reaction proceeded smoothly in under 3 hours affording dihydrocodeine (**118α**), but in only 37% yield.



2 **118α**

Scheme 14

Diimide reduction of a *E/Z* mixture **138** under similar reaction conditions required prolonged reaction time but gave a single product from TLC analysis. Subsequent work-up and purification by column chromatography gave compound **126** as a colourless oil in 56% yield. The ^{1}H-NMR spectrum however, did reveal the presence of trace amounts of the unreduced isomer ***E*-138** which would suggest a rate difference in reduction between the two geometrical alkenes.



126β **126α**

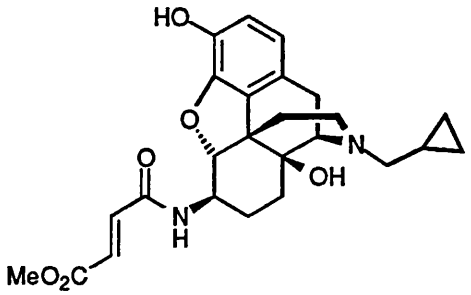
Although mass spectrometry, ^{1}H, and ^{13}C-NMR gave satisfactory evidence for compound **126**, we were still not at this stage, totally certain of the stereochemical

outcome of the reduction *i.e.* whether diimide reduction of the double bond had proceeded from the α face to give **126β** or from the β face yielding **126α**.

Data from the ^{1}H-NMR spectrum of **126**, in particular the coupling constant between H-5 and H-6 of 8.3Hz would normally be indicative of a substituent with the α-stereochemistry when applied to the codeine system (typical values are in the region of 7-8Hz, whilst β-substituents have coupling constants of 2-4Hz)[87]. However, this comparison is somewhat misleading as ring C of codeine is constrained in a boat conformation as a consequence of the 7,8-double bond, whereas in 7,8-dihydromorphinans, ring C lies in a chair conformation[88]. Thus, a correlation with a more accurate model such as 6α–dihydrocodeine (**118α**), obtained from diimide reduction of codeine (**Scheme 14**), was required. In this case the coupling constant is 5.3Hz and from this data we conclude that the cyclohexylmethyl group be β to the plane.

A nOeSY experiment indicated H-5 to be within 2-4Å of both H-15ax and H-15eq, but not to H-6 which again favours the cyclohexylmethyl substituent in the β position *i.e.* diimide reduction of **138** proceeds stereoselectively from the α face to afford **126β**.

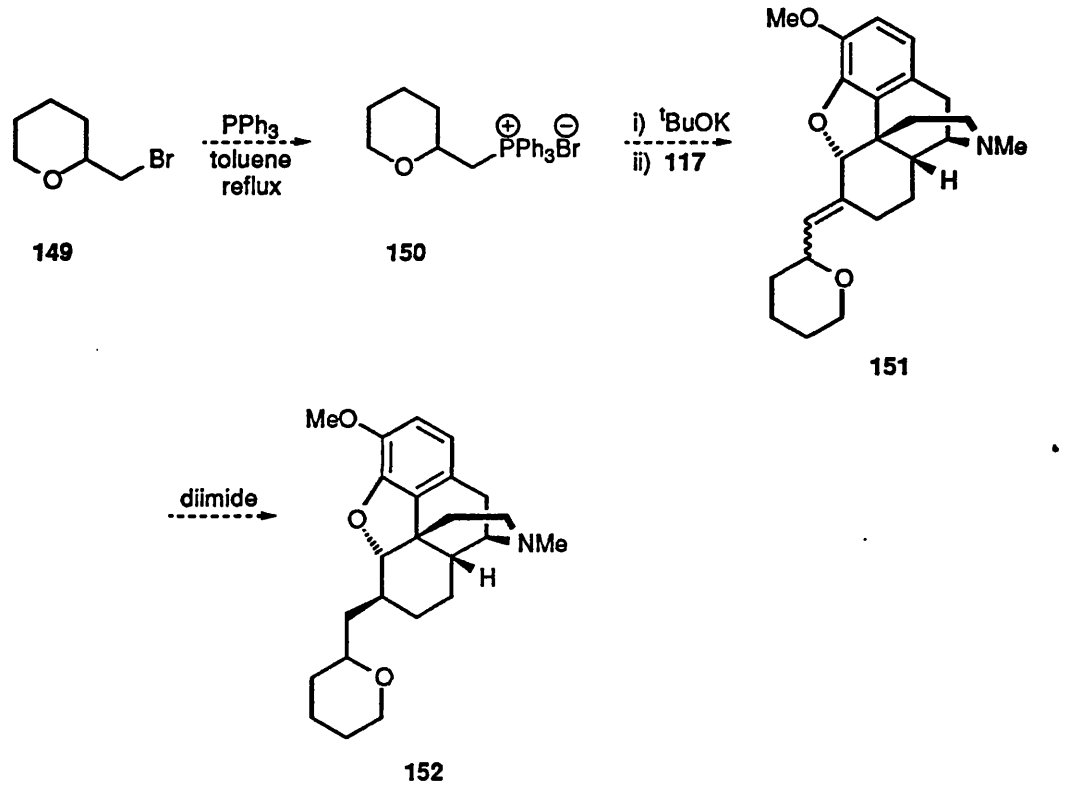
Although the reduction of **138** did not proceed as desired to give the α-stereochemistry at C-6, we were sufficiently encouraged by this result to search the literature for other morphine derivatives possessing substituents with the 6β-stereochemistry with a view to gaining an insight to the biological activity of such compounds. Suprisingly there are relatively few reports concerning compounds of this type.



148 (β-FNA)

The majority of examples are derived from isocodeine and include halides[87], substituted amines[89] and thiols[90] as well as methyl and several phenyl compounds[91]. In the dihydroisomorphine series, even fewer examples have been reported[92, 93] although of major importance is β-funaltrexamine[94] (**148**, β-FNA). This compound is used as a highly selective μ-receptor antagonist. Thus, to explore the analgesic properties of compounds with 6β-substituents, we decided to synthesise several other compounds of this type and to evaluate them for analgesic activity.

The synthetic route to the second of our targets, 6β-(tetrahydro-2H-pyran-2-yl)methyldihydrodeoxycodeine (**152**) is shown in **Scheme 15**.



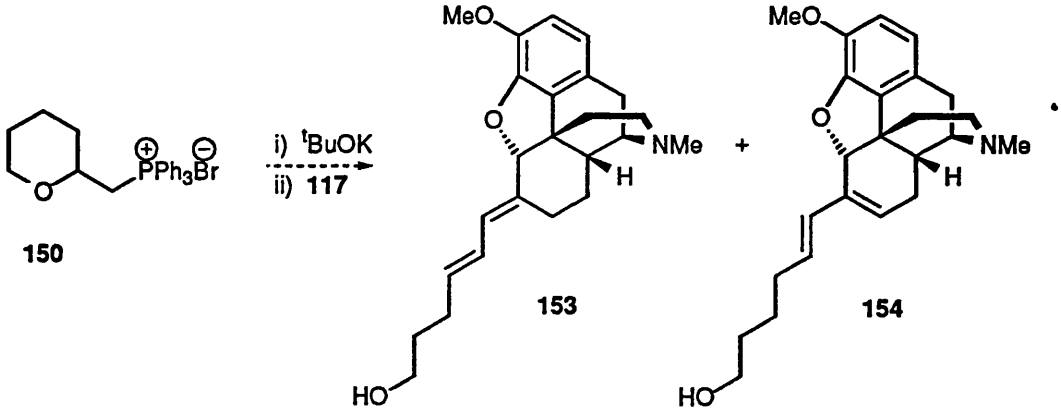
149 **150** **151** **152**

Scheme 15

Phosphonium salt **150** was obtained in a 69% yield as a colourless crystalline powder from the readily available (±)-2-(bromomethyl)tetrahydro-2H-pyran (**149**) by reaction with triphenylphosphine in boiling toluene. Subsequent Wittig reaction with dihydrocodeinone (**117**) gave three new components by TLC with similar R_f values in

an overall yield of 97%. Separation, by column chromatography, of the first two components (1:1 mixture of isomers by ^{1}H-NMR with R_f=0.28 and 0.26) proved unsuccessful but the third, more polar component (R_f=0.22) could be partially separated in the pure state.

Although we initially considered these products to be a *E:Z* diastereomeric mixture of **151**, this assumption was quashed when IR spectra of the single compound and also the mixture revealed a strong absorption band at 3172cm^{-1}, generally associated with an hydroxyl group. This data led us to believe that during the reaction, either the 4,5-ether ring of the 4,5-epoxymorphinan or the pyran ring of the side chain had been cleaved. Strong evidence suggesting the latter came from ^{1}H-NMR data of the single product which clearly indicated a singlet at δ4.90ppm associated with H-5 and therefore an unperturbed morphinan skeleton. More interesting, the ^{1}H-NMR spectrum showed 3 proton resonances in the olefinic/aromatic region of the spectrum with a spin coupling pattern characteristic of a conjugated diene system. We considered this collective evidence to favour **153** (**Scheme 16**). Nevertheless, it was not possible to ascertain whether the structure contained an exocyclic (**153**) or endocyclic (**154**) double bond, although it is likely that both compounds were present in the mixture.

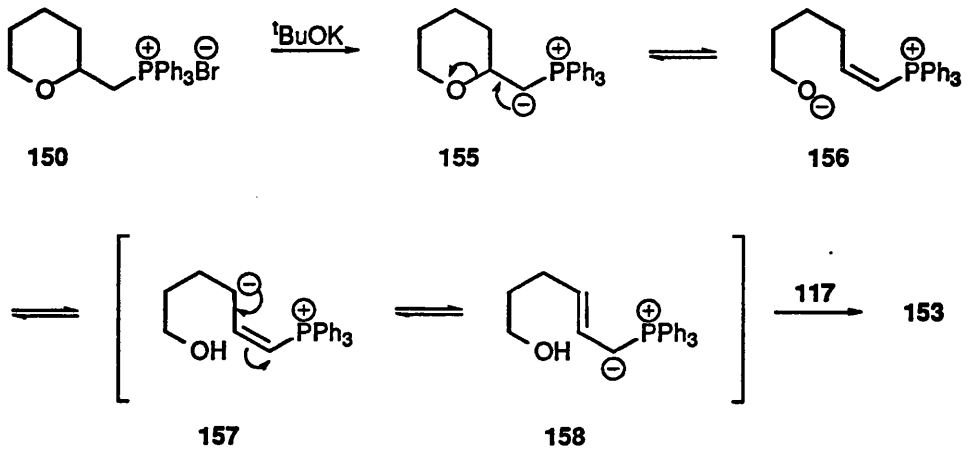


150 **153** **154**

Scheme 16

The possible mechanism of ring opening during the reaction is shown in **Scheme 17** and builds on observations made by Schweizer and co-workers[95] on a

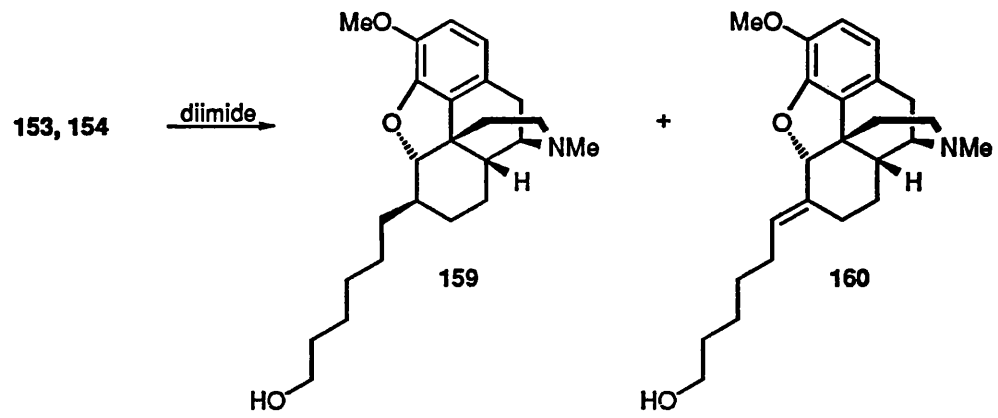
similar system. Ylide **155**, generated by base abstraction by potassium *tert*-butoxide of an acidic proton from salt **150**, undergoes ring opening to oxy anion **156**. This may then act as a intramolecular base and abstract an α proton from the β-substituted vinylic phosphonium salt **156** to give allylic ylide **157**. After rearrangement, **158** undergoes the normal Wittig reaction with dihydocodeinone (**117**) to yield product **153**.



150 **155** **156** **157** **158**

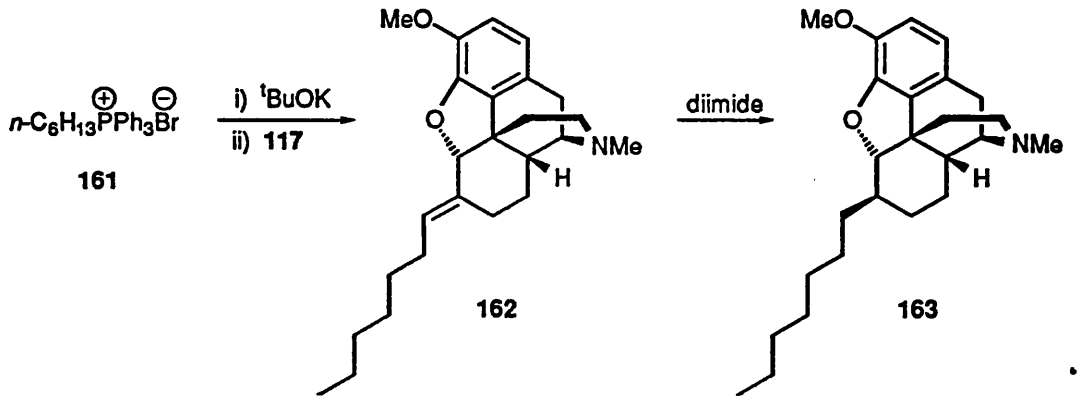
Scheme 17

Diimide reduction of an unseparated mixture of the three compounds gave as the major product, 6-(6-hydroxyhexyl)dihydrodeoxycodeine (**159**), although **160** was also isolated as a minor product. The stereochemistry of the carbon side chain at C-6 of **159** was assigned the β stereochemistry from the coupling constant between H-5 and H-6 (J=7.8Hz) which is comparable to that in the cyclohexylmethyl analogue **126β**. A confirmation of the absolute configuration of **159** came from an x-ray crystallography study (**Appendix 5.1.**).



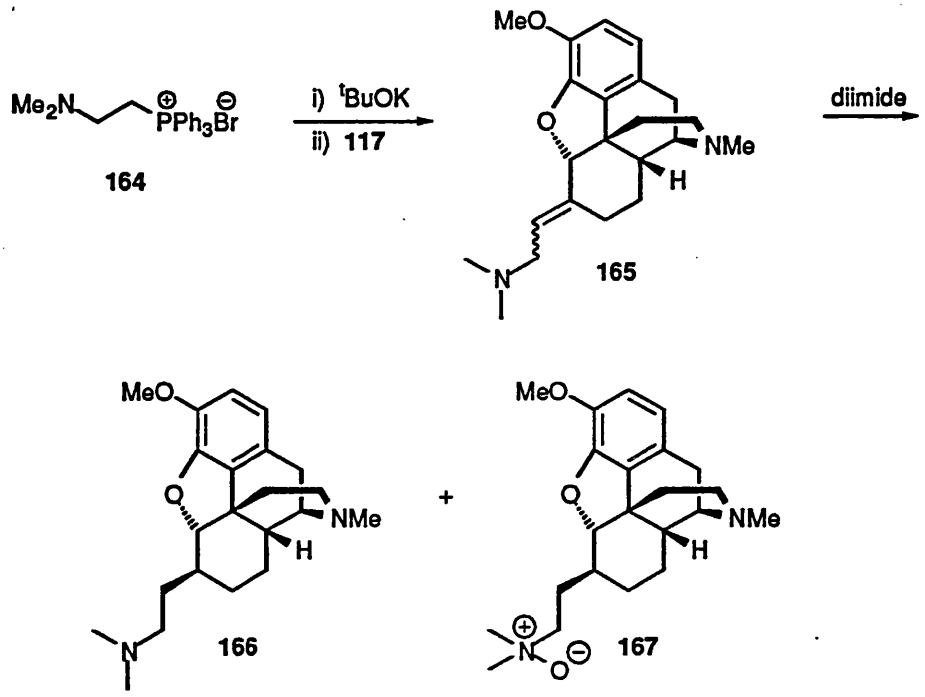
Scheme 18

Further compounds synthesised to assess the structure-activity relationships of the 6β alkyl substituents include 6-(*n*-hexyl)dihydrodeoxycodeine (**163**) and 6-(*N,N*-dimethylaminoethyl)dihydrodeoxycodeine (**166**). The former was obtained by Wittig reaction between dihydrocodeinone (**117**) and *n*-hexyltriphenylphosphonium bromide (**161**) and subsequent reduction of intermediate **162** (**Scheme 19**).



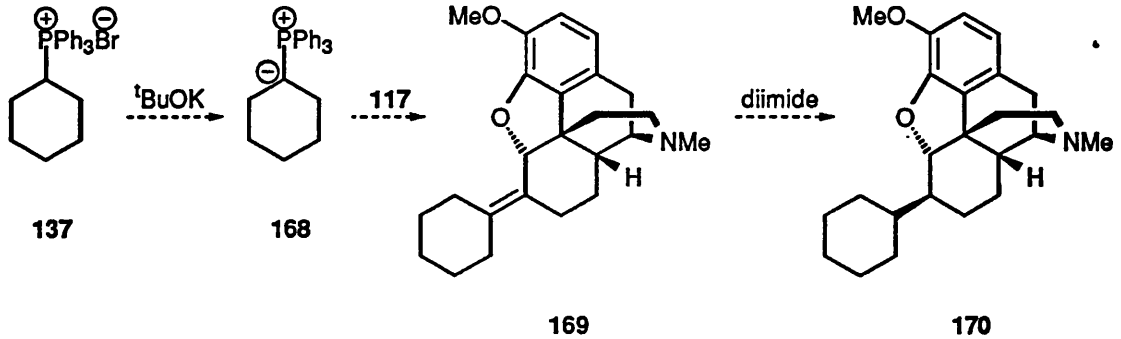
Scheme 19

The amino derivative was made by diimide reduction of a *E:Z* (8:1) mixture of **165**, formed on reacting **117** with readily available *N,N*-dimethylaminoethyltriphenylphosphonium bromide (**164**). Reduction of alkene **165** however, also gave rise to **167** as a minor product, the *N*-oxide generated presumably via oxidation of the amino side chain by the excess hydrogen peroxide required to oxidise hydrazine to diimide *in situ* (**Scheme 20**).



Scheme 20

Also of interest was the synthesis of the 6β-(cyclohexyl)dihydrodeoxycodeine (**170**) using the same Wittig methodology (**Scheme 21**). Our major concern however was the steric strain imposed by the tetrasubstituted double bond in compound **169** and whether this strain would inhibit the reaction between dihydrocodeinone (**117**) and the ylide **168**.



Scheme 21

Reaction of **117** with cyclohexyltriphenylphosphonium bromide (**137**) afforded a single new product, which from TLC analysis (R_f=0.20) was surprisingly

more polar than the starting ketone. From the ^{1}H- and ^{13}C-NMR spectra it became apparent that morphinene **169** had not formed but instead the data was suggestive of a dimeric morphinoid structure.

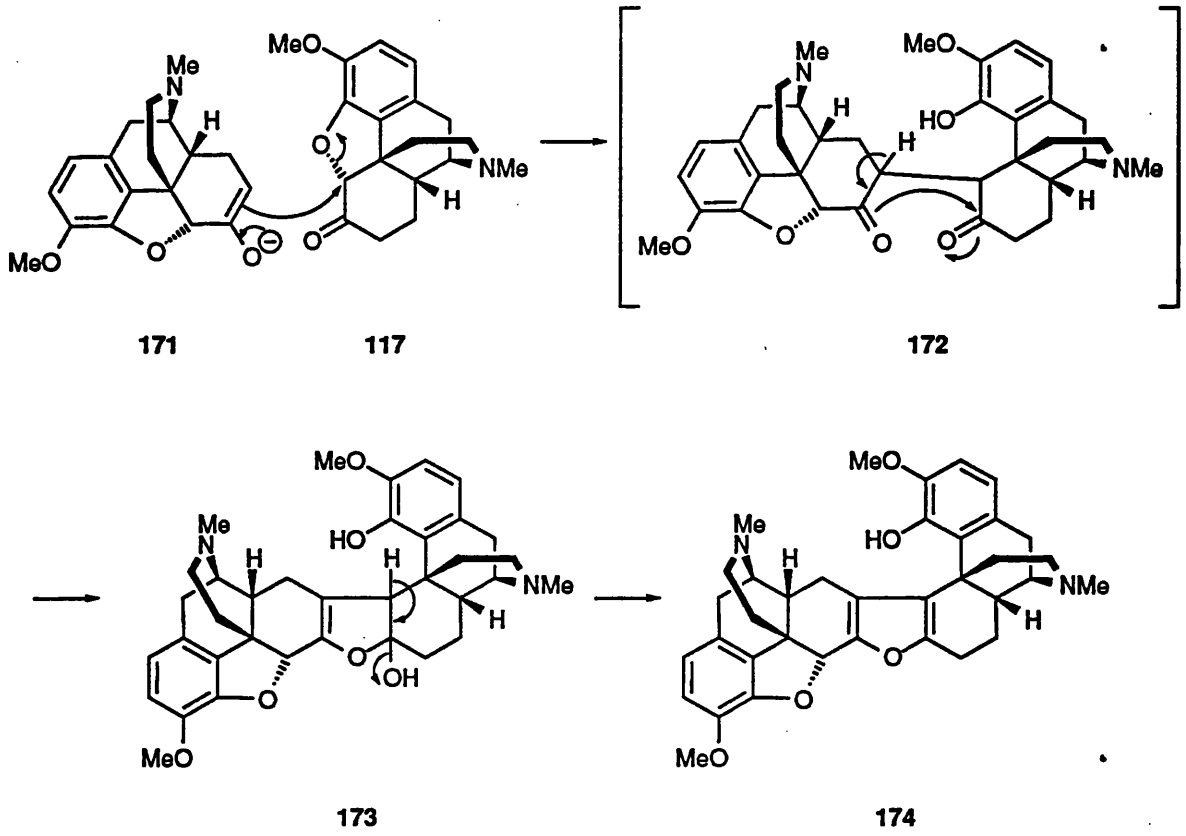
In the ^{1}H-NMR spectrum, the integration showed the presence of 42 protons including two *N*-methyl and two *O*-methyl signals at δ2.36, 2.37, 3.81 and 3.90ppm respectively. In the aromatic region of the spectrum four protons were present, corresponding to the protons at positions 1 and 2 of the morphine skeleton, but of added interest was the presence of only one proton signal at δ5.01ppm (singlet) for H-5. The absence of the second unperturbed H-5 signal in this region for the second dihydrocodeinone unit of the dimer suggests that ring cleavage at the ether bridge may have occurred during the reaction and that position 5 may be the point of linkage between the two molecules. A singlet at δ5.96ppm was also detected which could be exchanged with deuterium oxide thus revealing a hydroxyl functionality.

The dimer, for it was now clear that a coupling had occurred, showed 36 carbon signals in the ^{13}C-NMR spectrum. Notably absent was the presence of any carbonyl resonance at around δ200ppm and again only one signal at 91ppm, corresponding to the carbon at position 5 of an intact 4,5-epoxymorphinan, was present.

From the results of 90° and 135° DEPT experiments, this compound was shown to contain 4 methyl, 9 methylene, 10 methine and 13 quarternary carbons. Mass spectrometry data revealed a mass ion (base peak) at *m/z* 599 (M^{+}+H) confirming a bimorphine structure, and finally the IR spectrum showed the presence of a OH stretching band at 3333cm^{-1}.

From the aromatic region of the ^{1}H-NMR spectrum of this compound, it was apparent that traces of phosphorane were still present and so an attempt to remove this impurity was made. Acid extraction using dilute HCl however gave rise to a less polar compound (R_f=0.47) from TLC analysis. After work up, mass spectrometry data for this new product gave a mass ion at *m/z* 581 (M^{+}+H) showing a loss of 18 mass units which we attributed to the dehydration of water. It was observed from the

new ^{1}H-NMR spectrum that the hydroxy signal had shifted downfield from δ5.96ppm to δ7.46ppm. Treatment of this compound with ferric chloride solution gave a deep green colouration. This appeared to substantiate our initial idea of a phenolic group at position 4, which would have transpired from cleavage of one of the ether bonds of the dimer. From the 90° and 135° DEPT experiments determined on this product we observed that dehydration had caused a gain of one quarternary carbon at the expense of a methine giving 4 methyl, 9 methylene, 9 methine and 14 quarternary carbons.



171 117 172

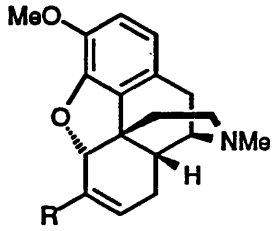
173 174

Scheme 22

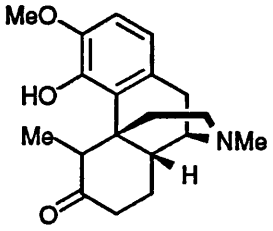
From the spectroscopic information we had gathered, we considered that the product initially formed from reaction between dihydrocodeinone (**117**) and ylide **168** was bimorphine **173**, which after treatment with dilute HCl, dehydrates to **174** as shown in **Scheme 22**. We believe that enolate **171** attacks a second molecule of dihydrocodeinone (**117**) and opens the ether ring at C-5 generating diketone

intermediate **172**. This subsequently undergoes cyclisation to the dihydrofuran derivative **173**.

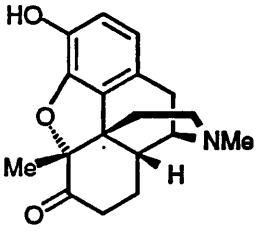
All three components, *i.e.* dihydrocodeinone (**117**), cyclohexyltriphenylphosphonium bromide (**137**) and potassium *tert*-butoxide, are required for the formation of **173** since separate reactions involving **117** and base in the absence of **137**, or reaction of **117** and **137** without potassium *tert*-butoxide, returned only unreacted starting material.



175 R=OMe
176 R=OAc
123 R=H

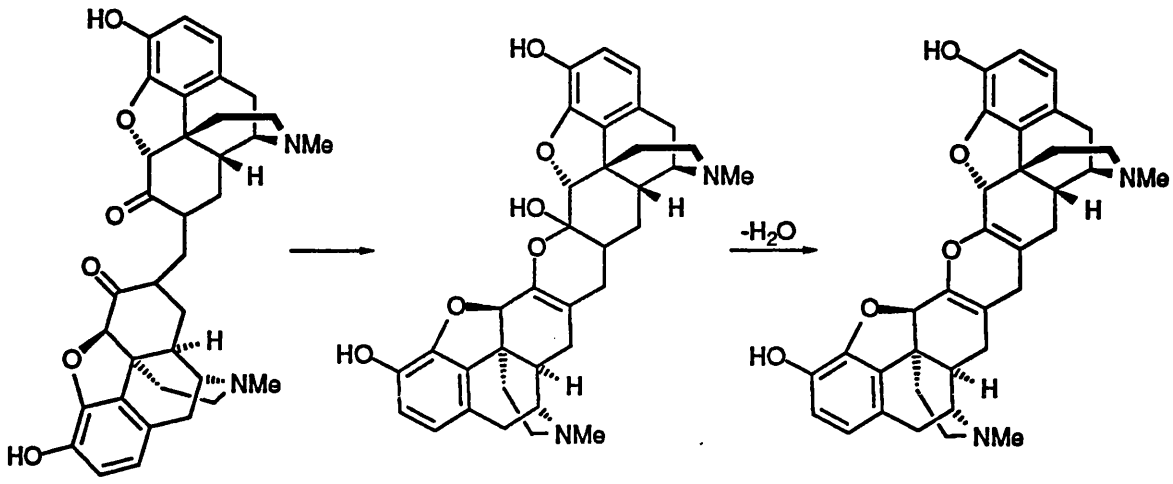


177



178

The attack at C-5 by carbanions is not entirely without precedent since it is known that dihydrothebaine[96] (**175**) reacts with methylmagnesium iodide to give 5-methyldihydrothebainone (**177**), used in the synthesis of metopon[97] (**178**). Dihydrocodeinone enol acetate[98] (**176**) and deoxycodeine C[99] (**123**) have also been reported to react with Grignard reagents to give ether ring opened products. Although it is often necessary in this type of reaction to have an unsaturation in the β,γ-position to the 4,5-ether oxygen atom (*i.e.* an allyl ether), Small and Rapoport have reported that dihydrocodeinone (**117**) behaves as a 6,7-unsaturated ether under forcing conditions to yield **177** on reaction with methylmagnesium iodide[100].

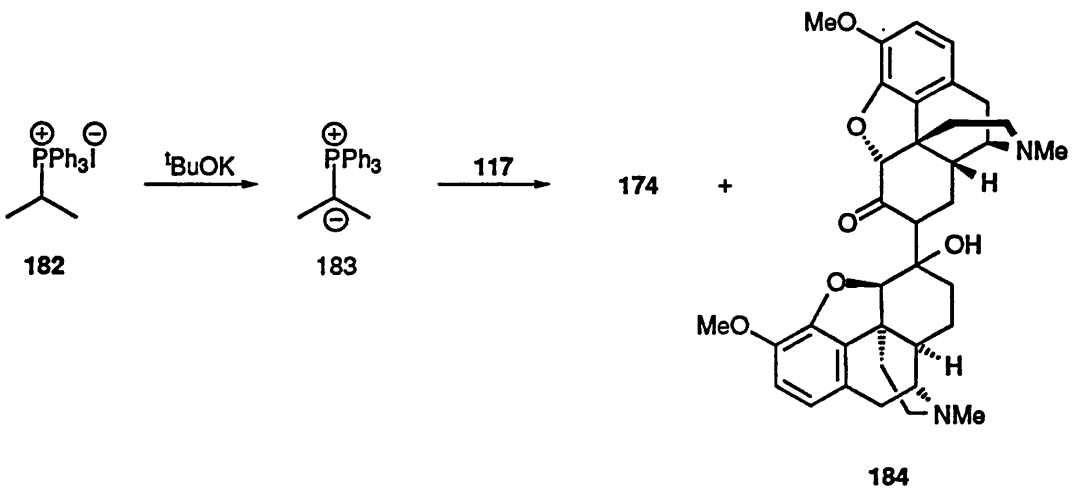


179 180 181

Scheme 23

Ring closures of the type **172** to **173** have also been recently described by Görlitzer[101] in the morphine series whereby diketone **179** cyclises to pyran **180** which then undergoes dehydration to bimorphinan **181** (**Scheme 23**).

We have also found that on replacing **137** with isopropyltriphenylphosphonium iodide (**182**), the Wittig reaction with dihydrocodeinone (**117**) also gives rise to the same bimorphinan **174**, although in reduced yield (**Scheme 24**). Also isolated from the reaction mixture was product **184**, formed by an aldol type condensation. Attempts to dehydrate **184** to the α,β-unsaturated analogue however failed, the reaction returning only **117**.



182 183 184

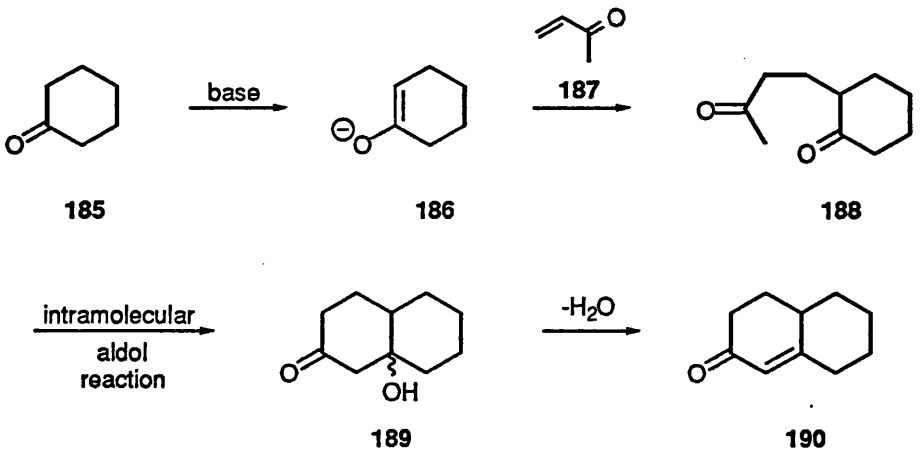
Scheme 24

Analgesia data from the effect of subcutaneous administration of some of these novel compounds in the mouse hot plate test are shown in **Appendix 5.2.** None of the compounds however showed significantly improved analgesic activity compared with the parent compound codeine (**2**).

2.3. The Robinson annulation

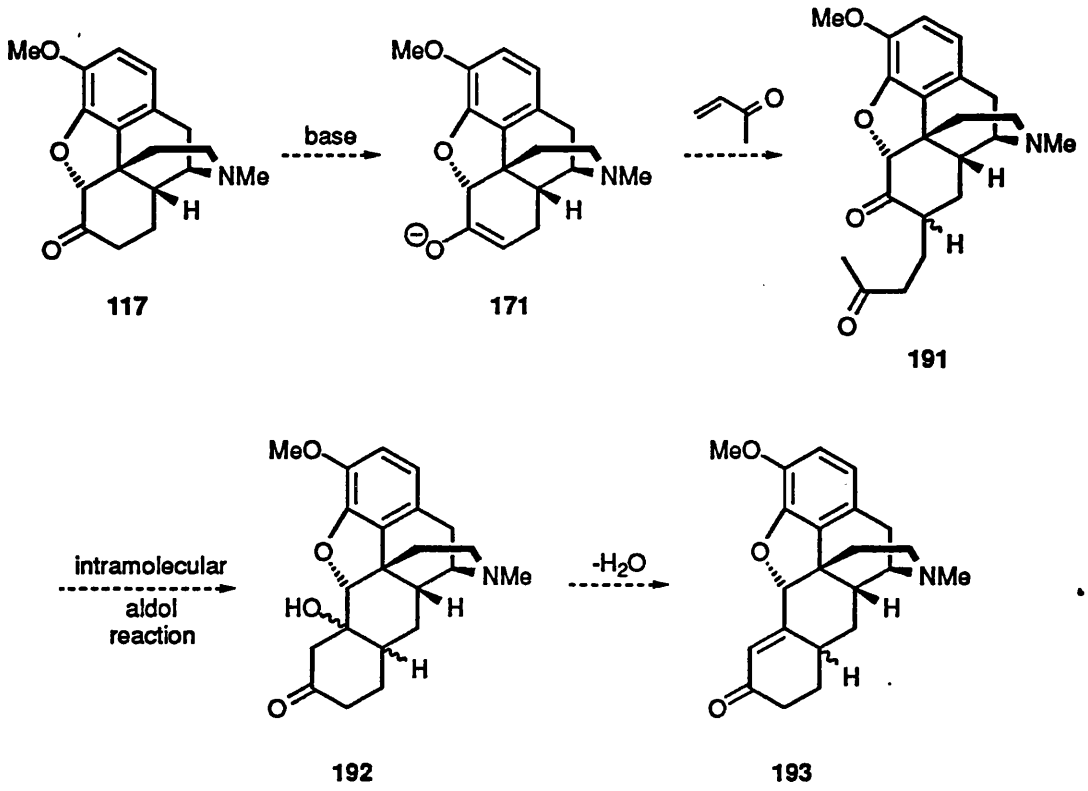
The Robinson annulation[102, 103], commonly employed in organic synthesis for the construction of polycyclic ring systems, offered a direct route to compounds possessing an enone ring system attached to C-6 and C-7 of the morphine skeleton. Furthermore, the functionality in this new ring system would provide an excellent opportunity for further transformations such as successive hydroxylation, thus approaching a fused mimic of glucuronic acid.

Many modifications of the annulation reaction have appeared in the literature since the publication of Robinson's original paper[104] in 1935, but the simplest procedure, using cyclohexanone (**185**) as an illustration (**Scheme 25**), involves the Michael addition of the enolate **186**, generated from **185** by proton extraction by a suitable base, to methylvinyl ketone (MVK, **187**). The intermediate diketone **188** then undergoes base-catalysed intramolecular aldol-type ring closure to the ketol **189**, which can be dehydrated to the enone **190** by treatment with either acid or base.



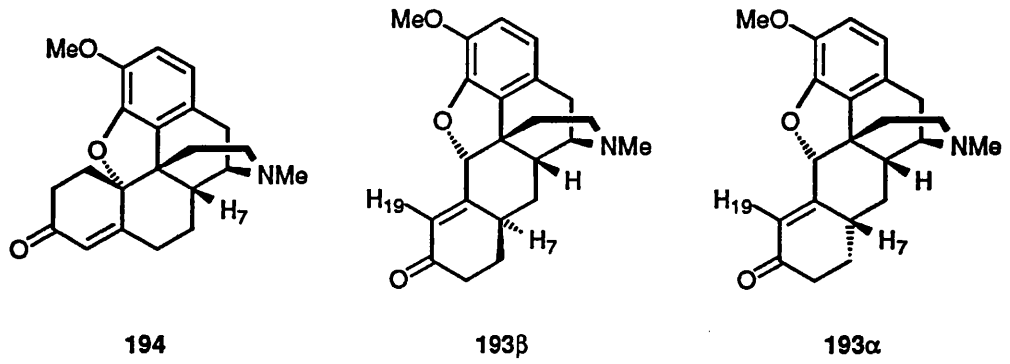
Scheme 25

The Robinson procedure, applied to our substrate, dihydrocodeinone (**117**), posed two intriguing questions concerning the regio- and stereochemical nature of enolate addition to the electrophile.



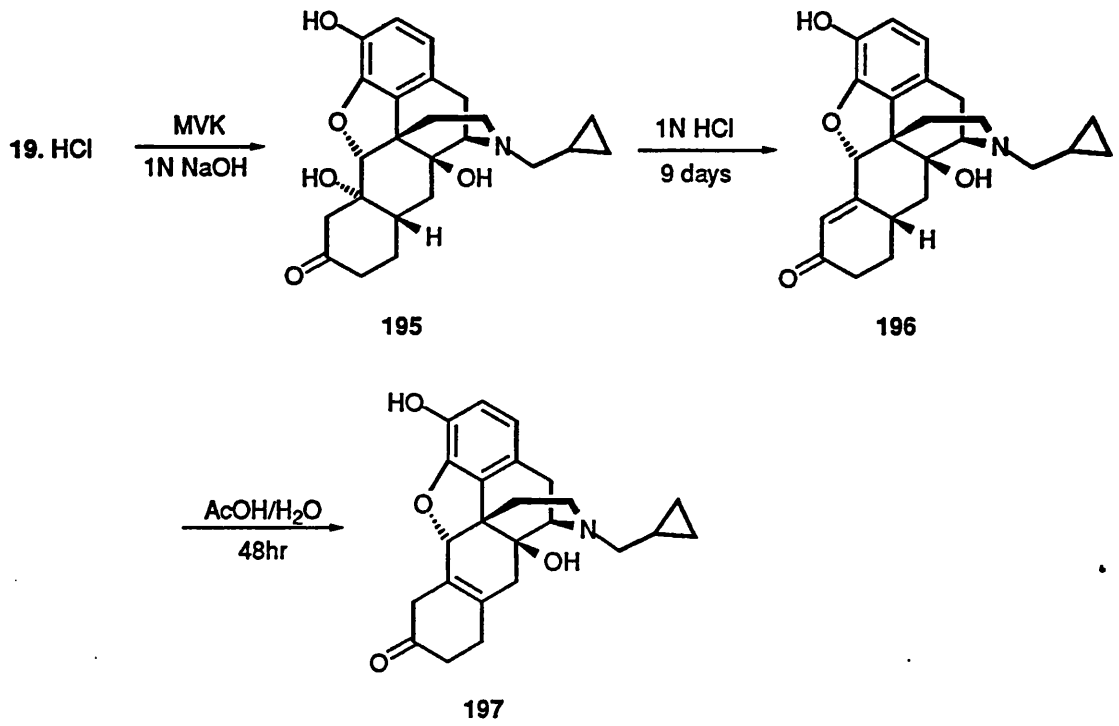
Scheme 26

With respect to the former, enolates generated from unsymmetrical ketones generally undergo alkylation regioselectively at the more highly substituted position under both acid and basic conditions[102] although this trend may be reversed as a result of severe steric interference at the more highly substituted α-carbon atom. In theory therefore, compound **194** may be generated. However, the formation of **194** requires base-catalysed abstraction of the proton at C-5 in dihydrocodeinone for which there is no literature precedent.



Secondly, depending on the stereochemical outcome of conjugate addition of enolate **171** to MVK, the proton at C-7 of the final product **193**, could possess one of two possible configurations in which H-7 is either below (α) the plane (relative to ring C), *i.e.* structure **193β** or structure **193α**, where it is above (β) the plane.

To date only a single application of the Robinson procedure in morphine chemistry has appeared in the literature. Portoghese and co-workers[105] claim that ketol **195** is formed in 80% yield from a reaction between naltrexone (**19**) hydrochloride and MVK (**Scheme 27**). Acid induced dehydration of **195** then affords the enone **196** in 65% yield which, on heating at reflux for 48 hours, isomerises to the β,γ-unsaturated product **197**. No biological activity data for these compounds were reported.



Scheme 27

The conditions used for the synthesis of ketol **195** were somewhat unusual in that the reaction was carried out in 1N sodium hydroxide solution. The Robinson annulation is normally performed in the presence of a strong base under anhydrous conditions.

Initially, following the procedure of Portoghese and co-workers, we reacted dihydrocodeinone (**117**) hydrochloride with MVK in methanolic 1N sodium hydroxide solution. After 14 hours, TLC analysis of the reaction mixture revealed the complete disappearance of starting material and the presence of two new compounds. The major product from the reaction proved however, to be the free base, dihydrocodeinone. Unfortunately the minor product was difficult to obtain in the pure state since it had a similar Rf value to dihydrocodeinone. Analysis of this compound thus depended on mass spectrometry, which showed a molecular ion peak at *m/z* 352, corresponding to compound **193**. Attempts to increase the yield of **193** by increasing the reaction time, temperature and quantity of MVK added were unsuccessful.

The failure to effect a clean Robinson annulation of dihydrocodeinone via the route described by Portoghese led us to re-investigate more conventional methods. An alternative approach developed by Marshall and Fanta[106] involves the generation of the ketone enolate using catalytic amounts of sodium ethoxide as base. In our hands, reaction of dihydrocodeinone with MVK at -10°C using a catalytic amount of sodium ethoxide showed little conversion of starting material. The presence of 4 new minor UV active components were nevertheless observed from TLC analysis. Separation of **193** from this mixture was achieved through column chromatography, although in low yield (4%).

Although at this stage IR, mass spectrometry, ^{1}H and ^{13}C-NMR data were in agreement with **193**, we were not as yet, certain of the stereochemistry at C-7 of the isolated product. A distinction between the two diastereoisomers was made from extended NMR spectroscopy studies.

Carbon signals were correlated with methylenes, methines or quarternary carbons by DEPT. ^{1}H-^{13}C-COSY analysis was employed to relate ^{1}H nuclei directly attached to the individual ^{13}C nuclei. From ^{1}H-^{1}H COSY measurement, the resonance of H-7 is coupled to both of the resonances of H-8α and H-22α; the signal of H-8α is coupled to the signal of H-8β and H-14; H-8β resonance is coupled to that of H-14; similarly the resonance of H-14 is coupled to that of H-9. Furthermore, the

resonance of H-22α is coupled to that of H-22β and H-21α; the resonance of H-22β is coupled to that of H-21β; and similarly the signal of H-21α to the signal of H-21β.

The 3-dimensional structural relationships between protons 5, 7, 8α, 8β, 9, 14, 21α, 21β, 22α and 22β were established from the nOe correlated 2D-NMR spectra. Thus, H-5 shows a close proximity to H-19; H-7 to H-8α and H-22β; H-8α to H-8β, H-10α and H-14; H-8β to H-14; H-9 to H-10α and H-14; H-22α to H-22β and H-21α; H-22β to H-21α.

Only structure **193**β, with H-7 in the α position, is consistent with the nOe data and the coupling constants between protons 8α, 8β, 9, 14, 22α, 22β. With respect to the latter, $J_{8\alpha,8\beta}$ is consistent with geminal coupling (13.9Hz); $J_{8\alpha,7}$ and $J_{8\alpha,14}$ are large (13.7 and 10.8Hz) and are in agreement to *cis* pseudo diaxial and axial-pseudo axial coupling respectively. $J_{8\beta,14}$ and $J_{8\beta,7}$ of 7.9 and 7.0Hz respectively are consistent with equatorial-axial and equatorial-equatorial couplings. Of further interest is the absence of any coupling between H-7, H-22β and H-22β, H-21α which is attributed to dihedral angles of approximately 90° between these two sets of protons. The above observations suggest that ring C of the opiate is in a half chair conformation while the new annulated ring is essentially planar. Compound **193**α was rejected as the possible structure because H-7 would be expected to exhibit an nOe with both H-8 and H-14 if its position was β to the plane. However, neither of the two relationships are observed in the 2D nOeSY spectrum.

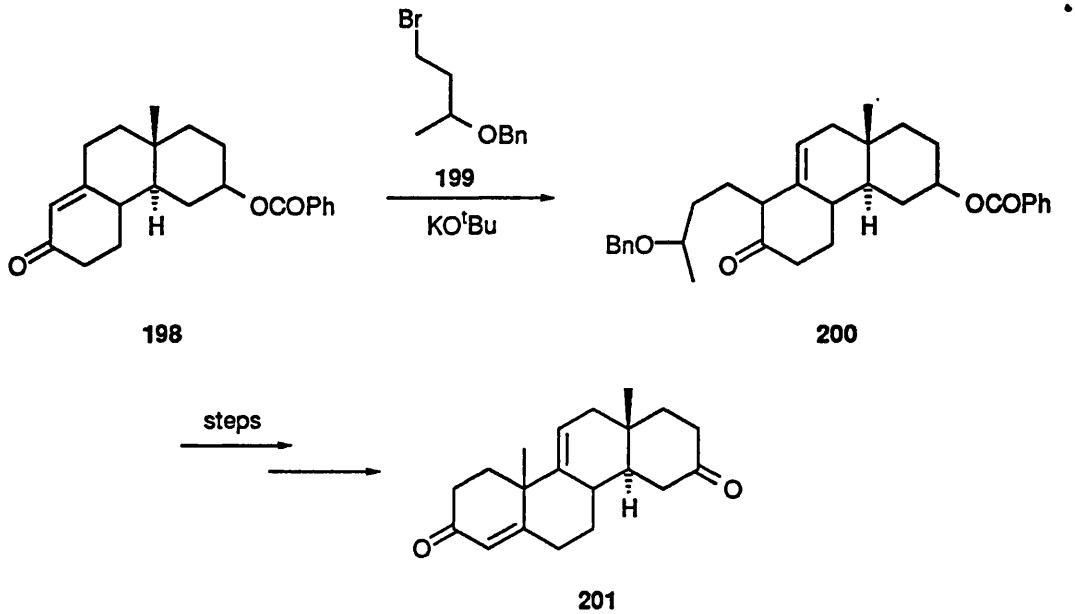
It is important to note that our assignment of the stereochemistry at C-7 for **193**β is the opposite of that for the same proton in Portoghese's naltrexone derivative **196**. The reason may be due to the steric effects exerted by the hydroxyl group at C-14 of naltrexone.

As the reaction had not gone to completion we decided to carry out a series of reactions varying the amount of base used to catalyse the annulation procedure. Attempts using 0.5, 0.7 and 1 equivalent of sodium ethoxide however showed no improvement. TLC analysis indicated either little conversion of starting material (0.5 and 0.7eq.) or decomposition (1eq.) of dihydrocodeinone. Similar results were

obtained using other bases such as sodium hydride and potassium *tert*-butoxide[107]. A final attempt at a lower temperature (-78°C) using lithium diisopropylamide (LDA) as base[108] yielded **193β** in only 3% yield.

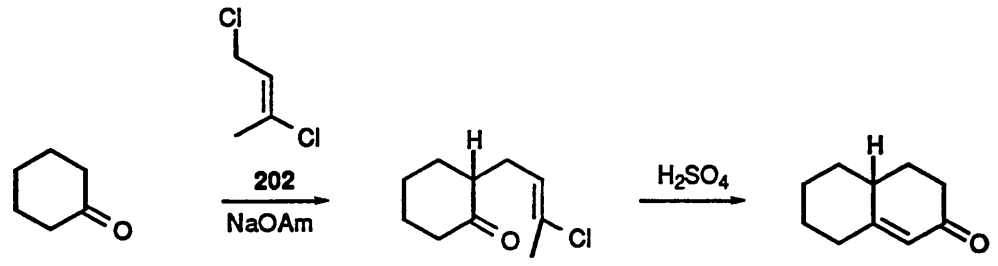
The low yield of **193β** obtained using 'standard' conditions for the Robinson annulation can generally be accounted for by the poor reactivity of the electrophile, *i.e.* MVK is not sufficiently reactive enough to trap the enolate. A further drawback commonly reported in the literature using MVK is that it is prone to polymerisation. In our case however, this was not observed. That these problems can, in part, be circumvented by direct alkylation using a more reactive electrophile such as an alkyl halide or allyl halide which possess a masked carbonyl functionality led us to examine this avenue.

Two examples (**Schemes 28 and 29**) of electrophiles which undergo the modified Robinson annulation are 1-bromo-3-benzyloxybutane (**199**) and 1,3-dichloro-2-butene (**202**), often referred to as the Wichterle reagent. In both cases the alkylated intermediates, **200** and **205** respectively, must be cyclised in a separate step which has the disadvantage of increasing the overall synthetic process.



198 200 201

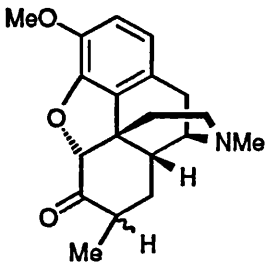
Scheme 28



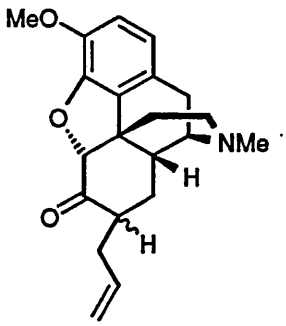
185 205 190

Scheme 29

Before using the above reagents, we decided to carry out a couple of model alkylations on dihydrocodeinone (**117**). Thus, using methyl iodide as a mimic for compound **199**, we attempted the synthesis of 7-(methyl)dihydrocodeinone (**204**) using LDA to generate enolate **171**. No coupling however, was observed on addition of methyl iodide and unreacted dihydrocodeinone was recovered. A similar attempt to prepare 7-(allyl)dihydrocodeinone (**205**) using allyl bromide also failed. These results using simple yet highly reactive electrophiles did not bode well for any future attempts and so this route was abandoned.



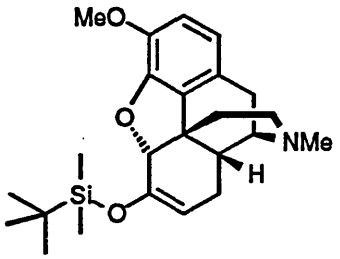
204



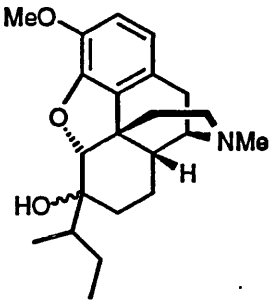
205

Reports that enolates generated from enol silyl ethers undergo alklation[109, 110] were also examined. Silyl enol ether **206** was initially prepared in 44% yield from a reaction between dihydrocodeinone (**117**) and *tert*-butyldimethylsilyl chloride using *sec*-butyl lithium as base. However, an appreciable amount (16%) of tertiary alcohol **207** was also isolated. This problem was overcome when the base was changed to a

more sterically hindered one. Thus, with LDA, the silylation reaction gave only **206** in 67% yield.

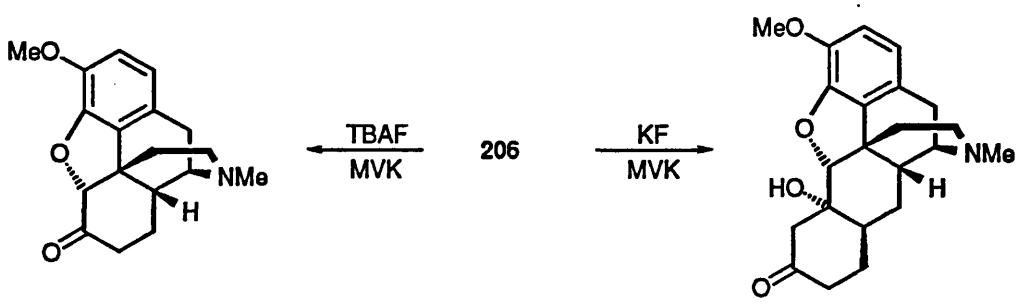


206



207

In the next step, cleavage of the silyl group to regenerate the enolate using tetrabutyl ammonium fluoride[111] in the presence of MVK however afforded only a near quantitative amount of our initial starting material dihydrocodeinone. Repetition of this reaction using an excess of MVK also failed. Surprisingly, on changing the fluoride source to anhydrous potassium fluoride[112], we were able to isolate the β-hydroxy ketone intermediate **192** in 15% yield. An attempt to form 7-(methyl)dihydrocodeinone (**204**) and 7-(allyl)dihydrocodeinone (**205**) by the same procedure failed however.



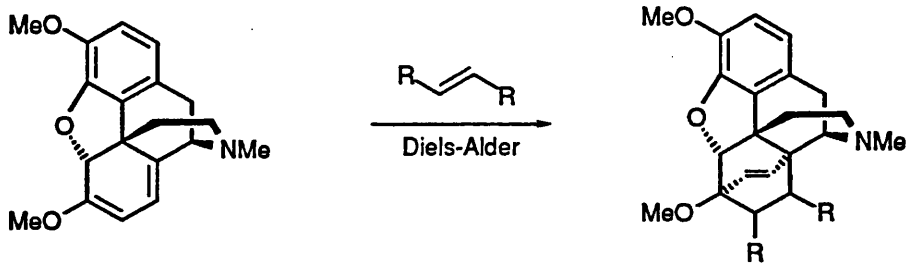
117 **192**

Scheme 30

In light of the poor yield for the Robinson annulation reaction and the failure of other electrophiles to couple with enolate **171**, we decided to search for an alternative route to compounds of this type.

2.4. Diels-Alder Reactions

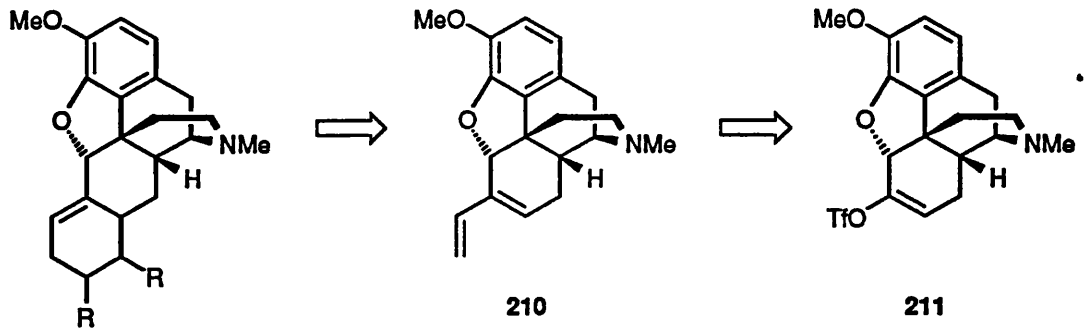
The failure to form cleanly a new six membered ring system fused to the C-6 and C-7 position of the morphine framework via the Robinson annulation led us to examine an alternative route to ring synthesis using the Diels-Alder methodology. In the field of morphine chemistry, Bentley and co-workers[13] first applied the Diels-Alder reaction to thebaine (3) in the 1960's for the synthesis of adducts with the general structure **208**. Here, the new cyclohexene ring is bridged across position C-6 and C-14 of the morphinan skeleton. Several compounds which possess this bridge structure, *e.g.* etorphine (**12**) and buprenorphine (**13**), have been shown to be potent analgesics.



3 **208**

Scheme 31

Although, in our case, the substituted cyclohexene ring system in target **209** (**Scheme 32**) is fused at positions C-6 and C-7 of the morphine framework, we envisaged that this may also be prepared via a Diels-Alder reaction between novel diene **210** and an appropriate dienophile. For the route to be viable therefore, a synthetic route to the key intermediate, diene **210**, was required. For this, we anticipated using a Stille[113] type cross-coupling reaction between vinyl triflate **211** and a suitable vinyl tin reagent.

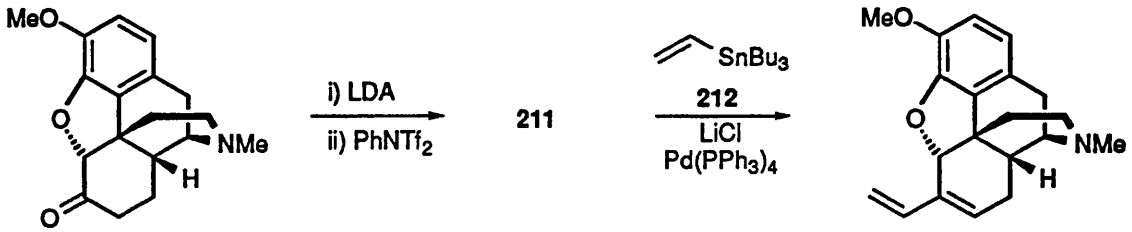


209 210 211

Scheme 32

Using the method of developed by McMurray[114], vinyl triflate **211** was prepared in 59% yield by trapping the enolate of dihydrocodeinone (**117**), generated using LDA as base, with *N*-phenyltrifluoromethanesulfonimide.

In the next step, cross-coupling of **211** with tri-*n*-butylvinyltin (**212**), previously prepared by a reaction between tri-*n*-butyltin chloride and vinylmagnesium bromide[115], under standard Stille conditions afforded successfully diene **210** in 90% yield. The structure of **210** was confirmed by a single crystal X-ray study (**Appendix 5.3**) and, in the crystal form, was shown to exhibit the *trans* configuration.

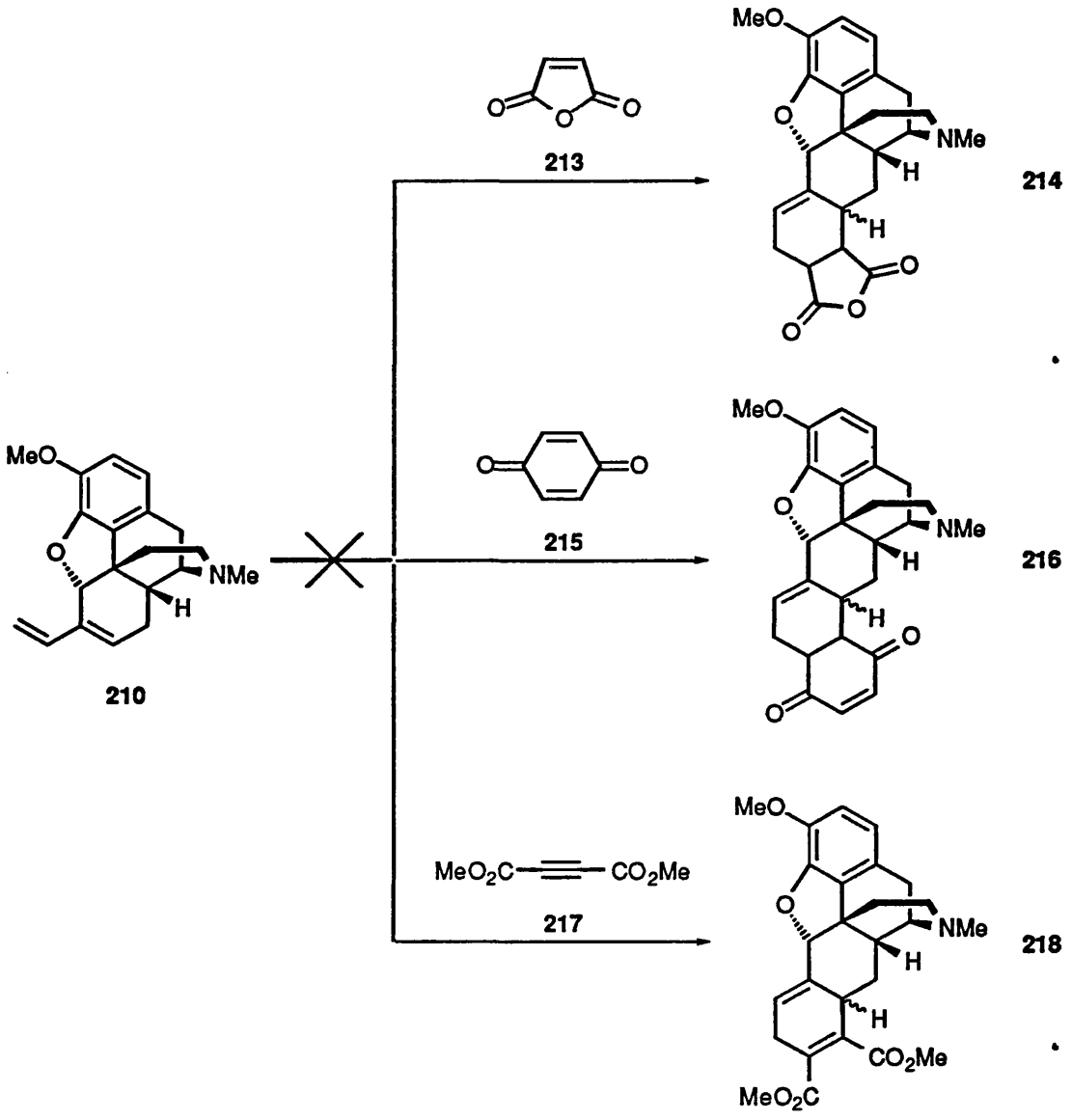


117 210

Scheme 33

To explore the reactivity of diene **210** in the Diels-Alder reaction, we decided initially to utilise simple symmetrical dienophiles as this would eliminate any problems concerning regioselectivity of addition. Thus, for preliminary investigations on our substrate, we chose maleic anhydride (**213**). Early reactions were however disappointing. Reaction of one equivalent of maleic anhydride with **210** at room

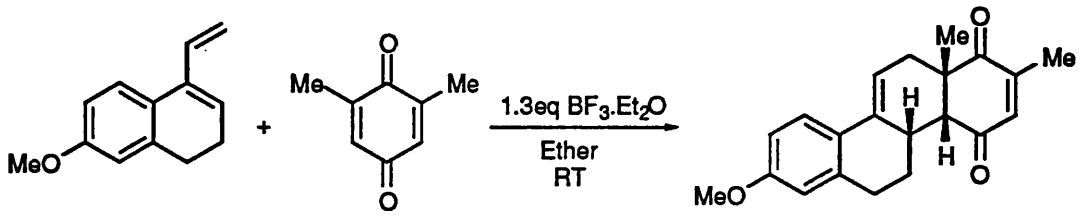
temperature gave no reaction by TLC, nor did heating the reagents in boiling toluene. The use of excess dienophile also failed to induce a reaction at room temperature or on heating. A report by Yates and Eaton[116] highlighting the use of aluminium chloride as a catalyst to accelerate the Diels-Alder reaction caused us to use similar conditions. However, the addition an equimolar quantity of $AlCl_3$ and also two equivalents of the Lewis acid failed to promote cycloaddition to give the adduct **214.**



Scheme 34

Undeterred by the negative results using maleic anhydride, we next carried out similar reactions using benzoquinone (**215**) and dimethyl acetylenedicarboxylate

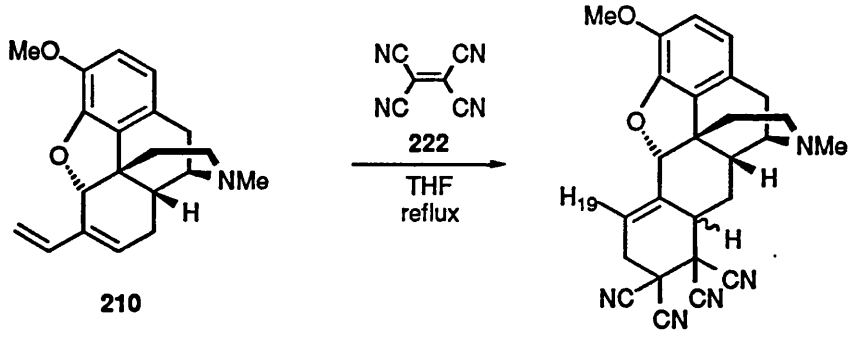
(217). With benzoquinone, no adduct was formed at room temperature or on heating a mixture of **210** and dienophile **215** in toluene at reflux. Addition of $AlCl_3$ to the reaction mixture also proved fruitless. Canadian workers have utilised boron trifluoride etherate[117] to catalyse a Diels-Alder reaction between substituted benzoquinone **220** and diene **219** (Scheme 35) and this method was also tried. In our case however, addition of $BF_3.Et_2O$ to the reaction mixture of **210** and benzoquinone yielded a tar which could not be purified.



219 **220** **221**

Scheme 35

Similar results were observed in the attempted preparation of the adduct **218.** Reaction of diene **210** with 1 equivalent of dimethyl acetylenedicarboxylate and later, an excess of the dienophile at both room temperature and on heating at reflux for 24 hours failed to cause a reaction. Attempted catalysis of the reaction with $AlCl_3$, boron trifluoride etherate and also tin chloride were unsuccessful and only starting material was recovered.



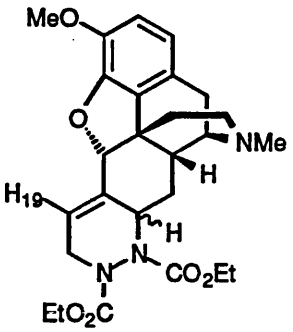
210 **223**

Scheme 36

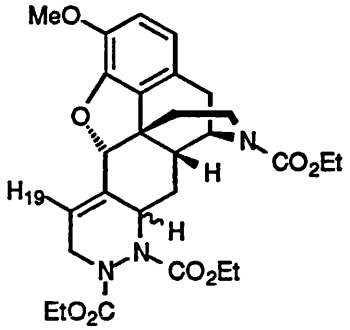
We next tried tetracyanoethylene (**222**, TCNE) since it is a powerful dienophile and has been reported to undergo the Diels-Alder addition readily with 1,3-dienes[118]. No conversion of starting material to adduct **223** was observed at room temperature after 24 hours although subsequent heating of this mixture for 2 hours in tetrahydrofuran resulted in the formation of a single new minor product with a retention factor higher than that of diene **210**. Attempts to increase the yield of the product by heating the mixture for a prolonged period of time (24 hr) was unsuccessful. Separation of this novel compound from the starting diene was achieved by column chromatography albeit in low yield (3%).

The identity of this adduct was initially confirmed by mass spectrometry which showed a molecular ion peak at *m/z* 438 ($M+H^+$) corresponding to the desired adduct **223**. The ^1H- and ^{13}C-NMR spectra were also in agreement with structure **223**. The ^1H-NMR spectrum, in particular, reveals the characteristic vinylic proton signal (H-19) at 6.09-6.14ppm. The stereochemistry of **223** at C-7 could not however, be determined by coupling data due to the extensive overlapping of the proton signals.

In the hope of gaining access to a heterocyclic ring system, we also attempted a Diels-Alder reaction between **210** and diethyl azodicarboxylate (**227**, DEAD). Yet again, reaction of diene **210** with 1 equivalent of diethyl azodicarboxylate at room temperature gave no reaction and on subsequent heating to 100°C, decomposition of the starting material was observed. Interestingly however, a reaction using 30 equivalents of DEAD at 100°C for 14 hours yielded two new compounds. These two products possessed similar R_f values from TLC analysis and could only be partially separated by column chromatography.



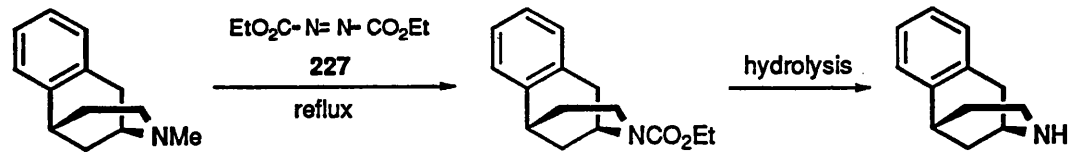
224



225

Although we had presumed initially that the reaction had furnished a diastereomeric mixture of the adduct **224**, the ^{1}H-NMR spectrum of the less polar component of the mixture possessed several idiosyncrasies which could not be accounted for by structure **224** alone. Firstly, the characteristic singlet which would normally be associated with the *N*-methyl protons at approximately δ2.45ppm was notably absent from the spectrum. Furthermore, from the integration pattern, it was apparent that this compound possessed five additional protons which, from the chemical shifts values, suggested an extra ethoxycarbonyl group. Collectively, these facts indicate strongly the formation of the ethyl carbamate adduct **225**. Mass spectrometry data obtained for this adduct revealed a molecular ion at *m/z* 541 ($M+H^+$), which is consistent with structure **225**.

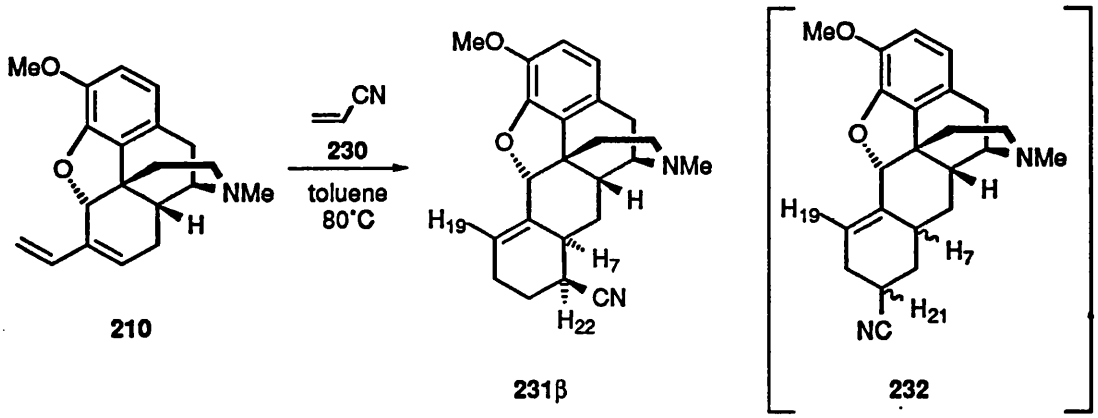
The formation of carbamates from tertiary amines using diethyl azodicarboxylate has been reported in the literature. For example, May and co-workers[119] have shown that ethyl carbamate derivative **228** may be prepared by heating together a mixture of *N*-methylbenzomorphan **226** and DEAD (**Scheme 37**). The intermediate was later hydrolysed to yield benzomorphan **229**. The overall route constitutes a method for the demethylation of tertiary amines.



226 228 229

Scheme 37

The limited success encountered using symmetrical dienophiles led us to turn our attention to Diels-Alder reactions involving unsymmetrical dienophiles. In the first instance we utilised acrylonitrile (**230**). Reaction of diene **210** with acryonitrile at 80°C in toluene, generated two new compounds although TLC analysis also revealed unreacted starting diene. Unfortunately, these two compounds possessed similar retention factors (R_f = 0.48 and 0.50) but we were able nevertheless to isolate, from the mixture, the less polar component in the pure state, albeit in low yield (9%).



210 231β 232

Scheme 38

It is apparent that with unsymmetrical dienophiles such as acrylonitrile, C-21 (**232**) and C-22 (**231β**) substituted derivatives could result. However, a differentiation between which of the two regioisomers we had isolated was made from a consideration of the coupling relationships between protons H-7, H-19, H-20, H-21 and H-22. Thus, if adduct **232** was formed, we would expect to observe H-7 coupled to the resonance of H-22 (methylene) which would in turn be coupled to that of H-21

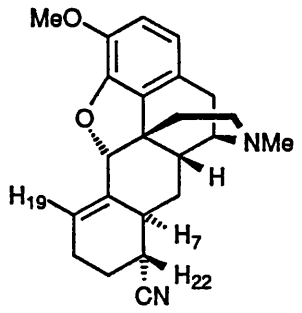
(methine). Signal H-21 would then be coupled to that of H-20 (methylene) which would be coupled to the vinylic proton resonance H-19 (methine). Conversely, for regioisomer **231β**, the signal H-7 would be coupled to that of H-22 (methine). Resonance H-22, in turn, would then be coupled to the resonance of H-21 (methylene) which is coupled to that of H-20 (methylene) which would be coupled to the vinylic proton signal H-19 (methine).

^{1}H-^{13}C-COSY analysis was initially used to relate ^{1}H nuclei directly attached to the individual ^{13}C nuclei. From the ^{1}H-^{1}H-COSY spectrum, the following coupling relationships were observed. The resonance of the vinylic proton, H-19, is coupled to that of H-20α. The signal H-20α in turn is coupled to that H-20β as well as to that of the resonance H-21β; H-20β resonance is coupled to H-21α; and that of H-21β is coupled to both the signals of H-21α and H-22; similarly the resonance H-21β is coupled to that of H-20β; and H-22 is also coupled to H-7. Other important relationships obtained from the ^{1}H-^{1}H-COSY spectrum concern protons H-7, H-8 and H-14. The resonance of H-7 is coupled to those of H-8α and H-8β; and the signal due to H-8α is coupled to H-8β and H-14; H-8β is coupled to H-14. The pertinent carbon atoms were correlated as methines and methylenes by 90° and 135° DEPT. Thus, the resonances of C-7, C-19 and C-22 are methines while those of C-20 and C-21 are methylenes. From the facts above, it is therefore clear that the isolated product of the cycloaddition reaction is regioisomer **231β**.

The stereochemistry at the two stereogenic centres, C-7 and C-22, were established from a combination of nOe correlated 2D-NMR spectra and the coupling constants between the appropriate protons. Thus with respect to the former, H-5 is within 2-4 Angströms of H-19. Similar distances separate H-7 from H-8α and H-22; H-8α from H-8β; H-8β from H-14; H-9 from H-14; H-19 from both H-20α and H-20β; H-20α from H-20β and H-21α. From molecular models, the nOe observed between H-7 and H-8α and the absence of an nOe between H-7 and H-8β renders H-7 as having the α configuration. Likewise, the nOe between H-7 and H-22 also fixes the latter proton with the α stereochemistry.

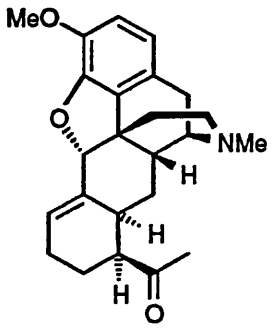
From the splitting pattern of the resonance of H-22 (ddd) at δ2.73ppm, coupling constants of 11.6Hz, 5.5Hz and 3.1Hz are observed. Thus, the first coupling constant would be indicative of a dihedral angle of <15° between H-22 and H-7 which is consistent with the nOe data in that both these two protons are in the α configuration; the last two coupling constants are consistent with dihedral angles of approximately 30° and 60° between H-22 and H-21β and H-21α respectively. From the considerations above, only structure **231β** is in agreement with all the relationships.

From MM2 calculations, it appears that diastereoisomer **231α**, with the cyano group α to the plane, is marginally favoured over that of **231β** (547 kcal.mol^{-1} versus 557 kcal.mol^{-1} respectively). These data were obtained by PC Spartan. They should not be regarded as absolute values of molecular stability, but simply as an indication of relative stability. Although the second compound in the reaction mixture could not be isolated, it is assumed that it is the diastereoisomer **231α**.

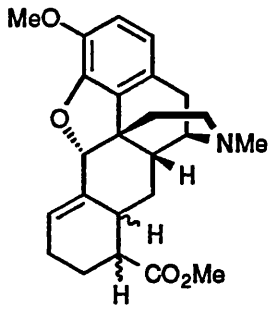


231α

We also attempted the Diels-Alder reactions with two further unsymmetrical dienophiles, methylvinyl ketone and methyl acrylate. In the case of the former, reaction with diene **210** afforded again a mixture of two products from which adduct **233** was isolated in 37% yield. With methyl acrylate two products were also generated in a total yield of 82%. These compounds however, could not separated by column chromatography and therefore from previous results, we presumed the products to be a mixture of adduct **234**.

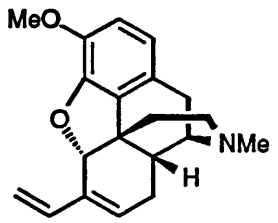


233

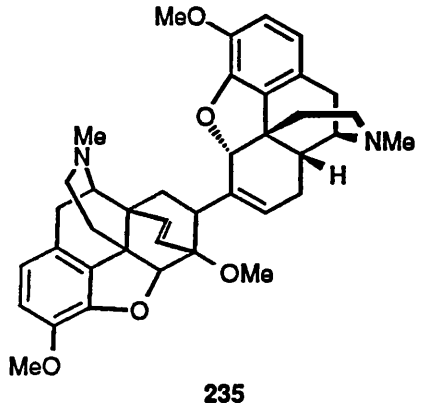


234

We also attempted a Diels-Alder reaction of **210** with thebaine (**3**) to form adduct **235**. This time, it was hoped that compound **210**, bearing an exocyclic double bond, would behave as the dienophile and thebaine as the highly reactive diene. However, a reaction between **3** and **210** at room temperature and in boiling toluene failed to occur and starting material was recovered.



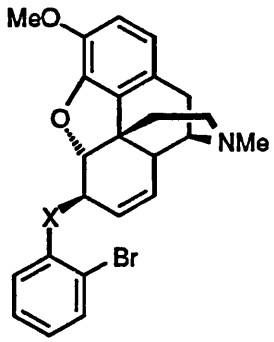
210



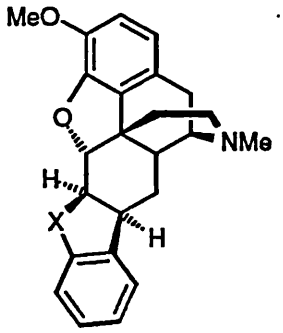
235

Scheme 39

2.5. Naltrindole Conjugates



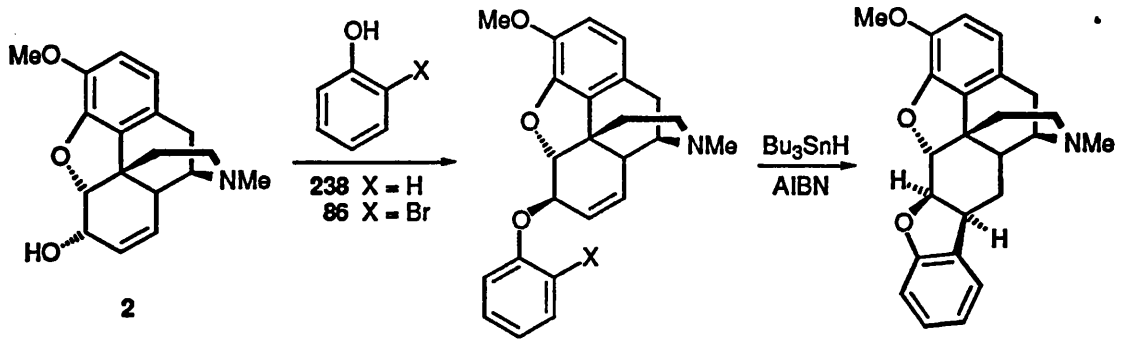
88 X = O
89 X = NH
236 X = S



82 X = O
83 X = NH
237 X = S

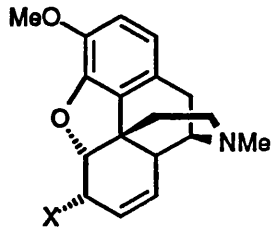
The Mitsunobu reaction[120], utilising the diethyl azodicarboxylate (DEAD)-triphenylphosphine (TPP) system, is a versatile method for the condensation of alcohols (ROH) and various nucleophiles (or acids, HA) to give the products (RA). This methodology has been employed successfully in the transformation of the 6α-hydroxy group of morphine and related compounds into 6β-hydroxy, 6β-amino, and 6β-thio derivatives via their corresponding benzoates, pthalimides, and thiolacetic acids[90, 121-123]. We considered that by using the appropriate substituted 2-bromobenzene we could, under similar conditions, generate intermediates **88, 89,** and **236** which could then be cyclised to the corresponding naltrindole conjugates **82, 83,** and **237.**

Concentrating on the route to the oxygenated compound **82,** we initially decided to carry out the coupling using phenol to determine the efficiency of the Mitsunobu reaction to form the alkyl aryl ether **239**[124, 125]. Reaction of codeine (**2**) with phenol (**238**) using 1.5 equivalents of the DEAD-TPP afforded 6β-(O-phenyl)codeine (**239**) albeit in low yield (17%).

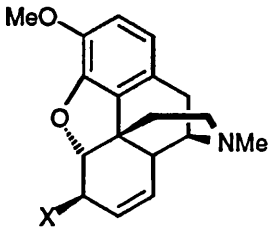


Scheme 40

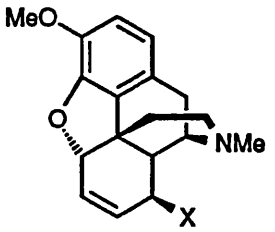
The β-stereochemical arrangement of the phenyl group of **239** was assigned from the coupling constants $J_{5,6}$ and $J_{6,7}$ (0.7 and 5.7Hz respectively) which are comparable with literature values for other 6β-substituted codeines[126]. In the next reaction, codeine was reacted with 2-bromophenol (**86**) under similar conditions to afford 6β-O-(2'-bromophenyl)codeine (**88**) in 41% yield. The chemical shifts of H-6 for both **239** and **88** (δ4.92 and δ4.95 respectively), when compared to isocodeine (**241**) (δ4.78), follow the trend of increasing downfield shift with increasing electronegativity of the substituent at the C-6 position.



240 X = $O\text{-}\overset{\oplus}{P}Ph_3$



241 X = OH
95β X = Br
242 X = $N(CO_2Et)NHCO_2Et$

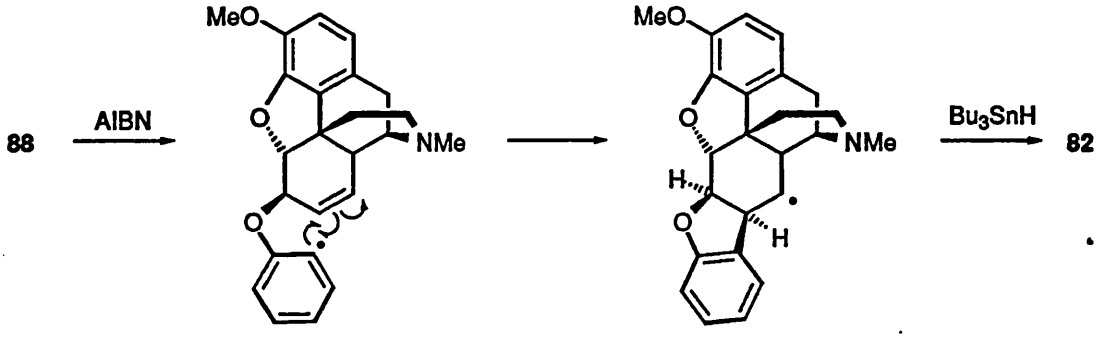


243 X = OC_6H_5
244 X = $O\text{-}oC_6H_5Br$
245 X = $N(CO_2Et)NHCO_2Et$

In both reactions the corresponding 8β-aryl products **243** and **244**, arising from a possible S_N2' displacement of triphenylphosphine oxide from the activated alcohol **240** were not detected. This follows the general trend observed for allylic alcohols in that Mitsunobu reactions principally proceed with clean inversion of stereochemistry

at the hydroxy carbon[127] although there are a few reported cases where S_N2' products are formed[128].

From examination of molecular models and by comparison with the behaviour of closely related systems in the literature[129, 130] we predicted that **88** would ring close to yield the 5,6-*cis*-fused product **82** via radicals **246** → **247**. Indeed, treatment of **88** with tri-*n*-butyltin hydride and AIBN under standard radical coupling conditions proceeded smoothly to afford target compound **82** in 90% yield.



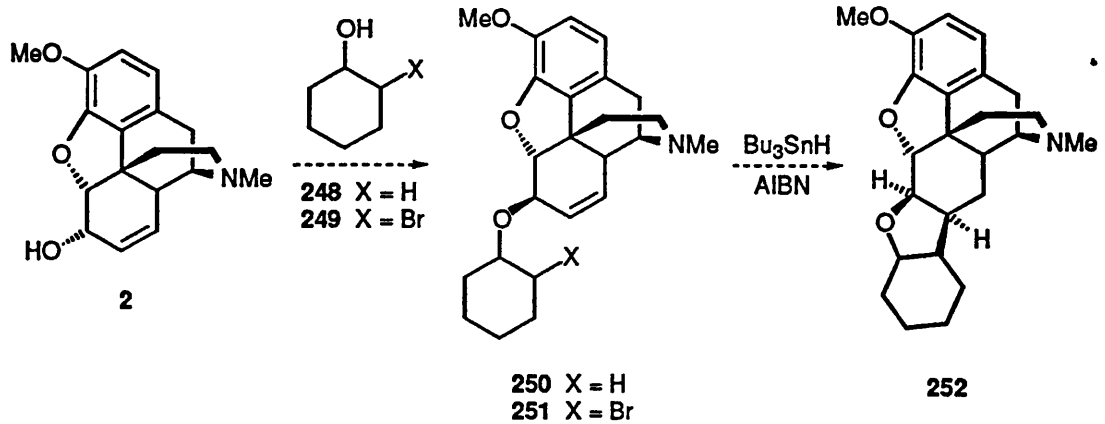
246 **247**

The stereochemistry of **82**, and in particular the geometry of the newly formed 2,3-dihydrobenzofuran ring, was firmly established by extended NMR spectroscopy experiments. Carbon signals were assigned as methylenes, methines or quarternary carbons by 90° and 135° DEPT. ^1H-^{13}C-COSY analysis was employed to relate ^1H nuclei directly attached to the individual ^{13}C nuclei. In addition, from ^1H-^1H COSY measurement, the resonance of H-5 is coupled to that of H-6; the signal of H-7 is coupled to both of the signals of H-6 and H-8_{ax}; and similarly the resonance of H-14 is coupled to both the resonances of H-8_{ax} and H-8_{eq}. The steric relationships between protons 5, 6, 7, 8_{ax}, 8_{eq} and 14 were established from the nOe correlated 2D-NMR spectra and were useful for elucidating the 3-dimensional structure. Thus, H-5 shows a close proximity to H-15_{ax} and H-15_{eq}; H-7 is between 2-4Å of H-6 and H-8_{ax}; and similar distances separate H-14 from H-8_{eq} and H-9.

Structure **82**, with the 2,3-dihydrobenzofuran ring at right angles to the ring C of the morphinan, is consistent with both the nOe data and the coupling constants

between protons 5, 6, 7, 8_{ax}, 8_{eq} and 14. With respect to the latter, $J_{14,8ax}$ is consistent with *trans* diaxial coupling (13.7Hz); $J_{14,9}$ and $J_{14,8eq}$ are relatively small (2.9Hz and 3.4Hz respectively) and are consistent with axial-equatorial coupling. The coupling constant between H-7 and H-8_{ax} of 7.3Hz is again due to equatorial-axial coupling whilst the absence of any coupling with H-8_{eq} is presumably due to a dihedral angle of approximately 90°. A dihedral angle of approximately <30° would account for the coupling constant of 9.3Hz between proton 6 and 7. The small coupling constant between H-5 and H-6 (2.0Hz) is consistent with isomorphine type compounds where the 6 substituent is electronegative and β to the plane. Molecular modelling and minimisation studies also show structure **82** to be consistent with the NMR data.

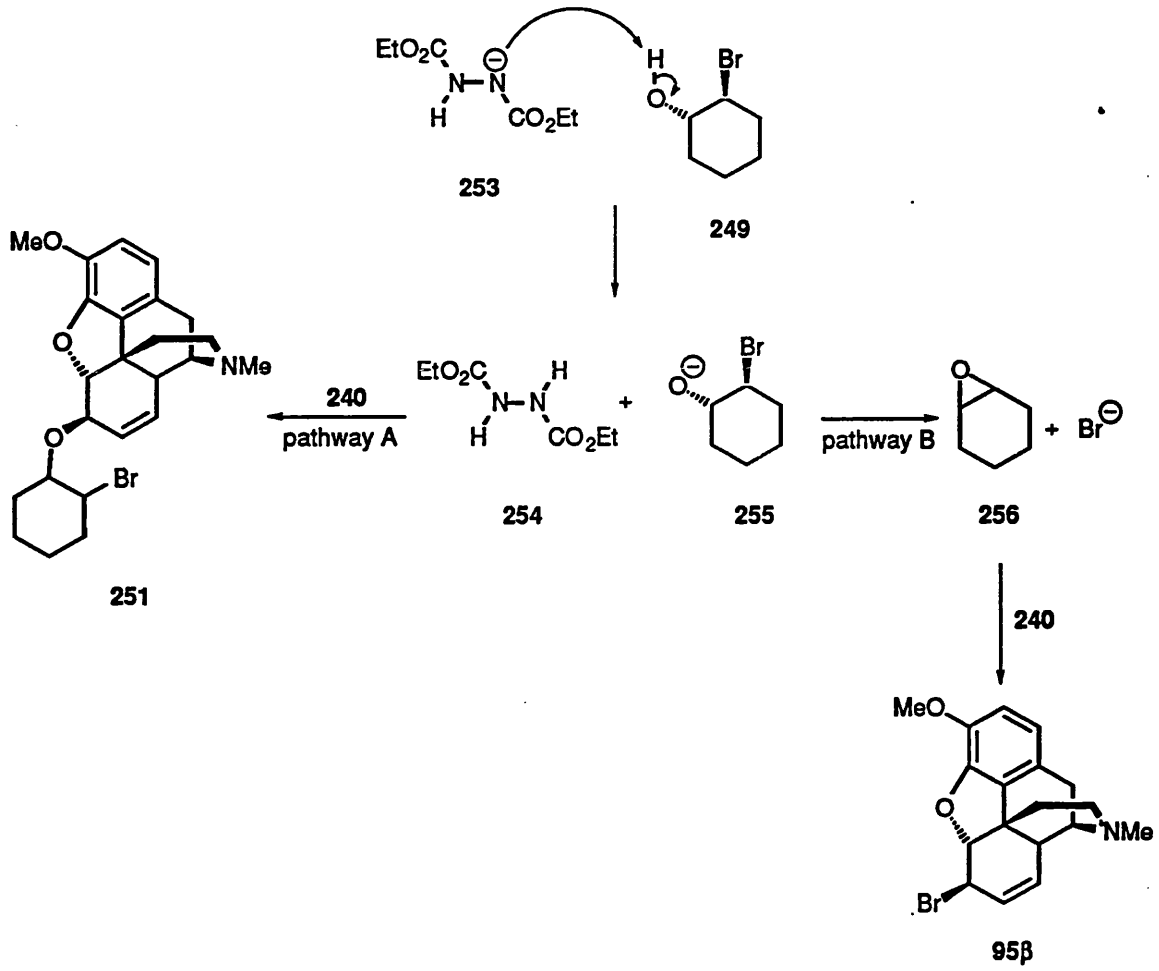
The successful synthesis of compound **82** prompted us to examine the possibility of using the same methodology to prepare the fully saturated analogue **252.** Our main concern was the acidity of 2-bromocyclohexanol (**249**). It has been reported that when the pK_a of the hydrogen in the acidic component (HA) is larger than 11, the yield of product RA is reduced considerably, or the desired reaction does not proceed[131]. Our fears were realised when we attempted a model reaction using cyclohexanol (**248**). A reaction of codeine with **248**, using 1 and also 1.5 equivalents of TPP-DEAD failed to give any coupled product. However, with 3 equivalents of TPP-DEAD we were able to isolate from the reaction 8β-(1,2-dicarbethoxyhydrazine)deoxypseudocodeine (**245**) in low yield (11%).



Scheme 41

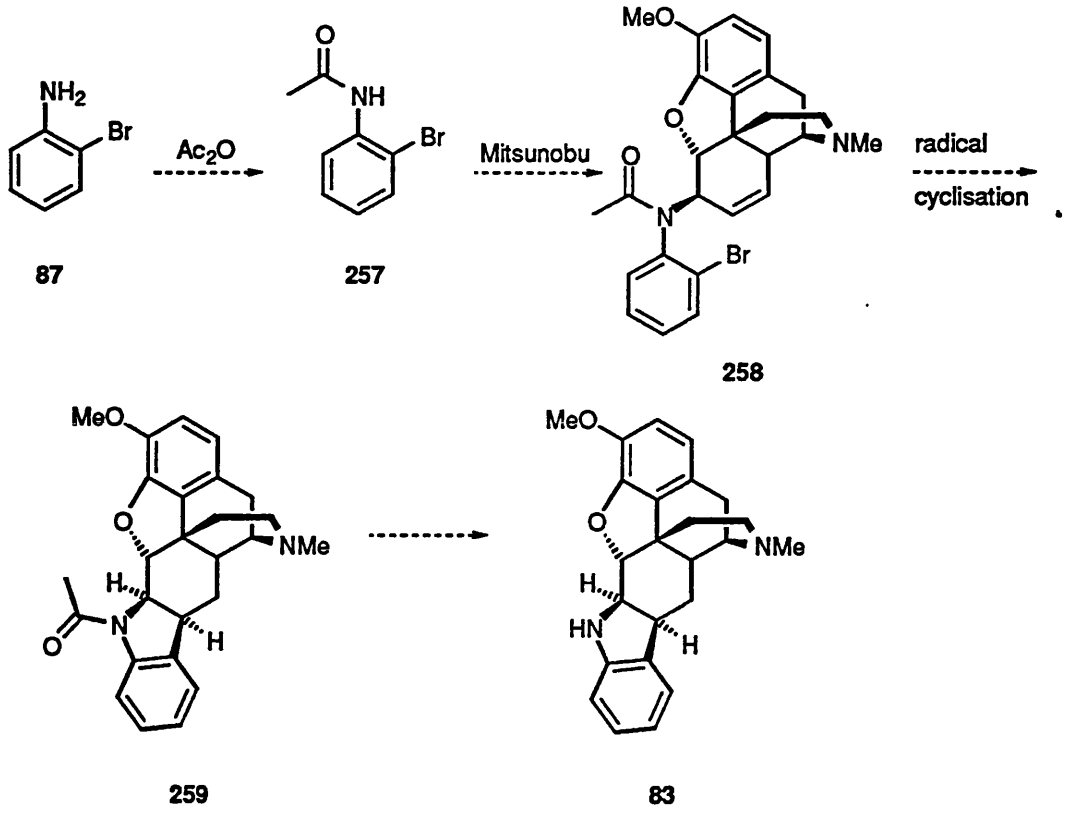
This can be explained by the fact that in the absence of an acidic component (HA) in the Mitsunobu reaction, *N,N'*-diethoxycarbonyl(dialkoxycarbonyl)hydrazines are produced[132], thus, S_N2' displacement of triphenylphosphine oxide by hydrazine anion **253**, as opposed to the usual S_N2 pathway, is favoured presumably by steric effects.

Although the coupling reaction with cyclohexanol was unsuccessful we decided to attempt the same coupling using *trans*-2-bromocyclohexanol (**249**), prepared from cyclohexene with aqueous *N*-bromosuccinimide[133], in the hope that this substrate would be sufficiently acidic for the product **251** to form. The reaction was again unsuccessful. No coupled product was isolated from the reaction between codeine and **249** but we were however, able to isolate from the reaction mixture 6β-bromocodide (**95β**) in 16% yield. The postulated mechanism for its formation is shown in **Scheme 42**. Proton abstraction from **249** by hydrazide anion **253** generates the alkoxide species **255**. This species undergoes intramolecular S_N2 displacement of bromide to generate cyclohexene oxide (**256**) in preference to intermolecular S_N2 displacement of triphenylphosphine oxide from activated species **240** to yield **251**. Finally it seems probable that bromide ion released in the process reacts with codeine or an equivalent to form 6β-bromocodide (**95β**)[134] .



Scheme 42

By changing the aryl substrate from 2-bromophenol (**86**) to 2-bromoaniline (**87**), we anticipated that the nitrogenous analogue **83** could be obtained. Sammes[135] had previously reported the synthesis of *N*-benzylaniline by the coupling of aniline and benzyl alcohol under Mitsunobu conditions but the yield was significantly poor due to the inability of the amino group to transfer a proton to the hydrazine anion. However, since time was against us we attempted the reaction between codeine and **87** using 1.5 equivalents of TPP-DEAD. After 40 hours, no reaction was observed by TLC and codeine was recovered quantitatively. For future work we considered that the acidity of the amino group could be increased by the acetylation of 2-bromoaniline (**Scheme 43**). The Mitsunobu coupling could then be repeated with the *N*-acyl-2-bromoaniline derivative (**257**). Radical cyclisation of intermediate **258** and subsequent removal of the acyl group would afford the desired compound **83**.


NH2
Br
Ac2O
O
NH
Br
Mitsunobu
MeO
O
NMe
O
N
Br
radical
cyclisation
87
257
258
MeO
O
NMe
H
N
O
H
259
MeO
O
NMe
H
HN
H
83

Scheme 43

CHAPTER 3

EXPERIMENTAL

General

All solvents were dried and distilled before use. 'Petroleum ether' refers to petroleum ether boiling in the range 60-80°C. Column chromatography was performed using Amicon Matrix 60Å silica gel under medium pressure using a small hand bellows. Thin layer chromatography was performed using aluminium backed 250μm silica gel plates containing fluorescent indicator. Visualisation was achieved by illumination under short wavelength (254nm) ultra violet light where possible or developed by treatment with a 0.5% potassium permanganate, followed by warming the plate.

Melting points were determined on Electrothermal Mk III apparatus and are uncorrected. Mass spectra were recorded on a VG7070E mass spectrometer. Elemental micro-analysis were carried out using a Carlo-Erba elemental analyser. Infrared spectra were recorded in the range 4000-600cm^{-1} using a Perkin-Elmer 1310 spectrometer.

^{1}H- and ^{13}C-nuclear magnetic resonance spectra were recorded on a Jeol GX270 (270MHz) or Jeol GX400 (400MHz) spectrometer. For ^{13}C, the operating frequency was 67.8MHz, using 90° and 135° DEPT pulse sequences to aid multiplicity determinations. Samples were prepared in solutions of deuterated chloroform. δ Values are expressed as parts per million downfield from tetramethylsilane (internal standard).

Codeine (2)

R_f = 0.25 ($CHCl_3$:MeOH = 9:1); Mp. = 156-157°C; IR (Nujol) : 3111 (OH), 1652 (C=C), 1635, 1606 (ArC-C), 1500 (C-N), 1273 (ArC-O-CH_3), 1055 (C-O-C) cm^{-1}.

δ_H (270MHz) : 1.78 (1H, dm, J_{gem} = 12.8Hz, H-15_{eq}), 2.06 (1H, td, J_{gem} = 12.8Hz and $J_{15,16}$ = 5.1Hz, H-15_{ax}), 2.30 (1H, dd, J_{gem} = 18.7Hz and $J_{10\alpha,9}$ = 6.2Hz, H-10α), 2.36 (1H, dd, J_{gem} = 12.6Hz and $J_{16,15}$ = 5.6Hz, H-16_{ax}), 2.44 (3H, s, N-$C\underline{H}_3$), 2.59 (1H, dm, J_{gem} = 12.5Hz, H-16_{eq}), 2.67 (1H, m, H-14), 2.90 (1H, br. s, OH), 3.05 (1H, d, J_{gem} = 18.6Hz, H-10β), 3.35 (1H, dd, $J_{9,10}$ = 5.9Hz and $J_{9,14}$ = 3.3Hz, H-9), 3.84 (3H, s, O-$C\underline{H}_3$), 4.18 (1H, m, H-6), 4.90 (1H, d, $J_{5,6}$ = 6.6Hz, H-5), 5.30 (1H, dd, $J_{8,7}$ = 9.9Hz and $J_{8,14}$ = 2.6Hz, H-8), 5.71 (1H, dm, $J_{7,8}$ = 9.9Hz, H-7), 6.65 (1H, d, $J_{1,2}$ = 8.2Hz, H-1), 6.72 (1H, d, $J_{2,1}$ = 8.2Hz, H-2).

δ_C (400MHz) : 20.38 (C-10), 35.40 (C-15), 40.33 (C-14), 42.76 (N-$\underline{C}H_3$), 42.90 (C-13), 46.28 (C-16), 56.18 (O-$\underline{C}H_3$), 58.76 (C-9), 66.18 (C-6), 91.15 (C-5), 112.81 (C-2), 119.39 (C-1), 126.71 (C-11), 131.10 (C-12), 142.12 (C-3), 146.17 (C-4).

Bromination of codeine[69]

To a stirred solution of codeine (930mg, 3.1mmol) dissolved in DCM (7ml) was added phosphorus tribromide (0.45ml, 4.7mmol). A pale yellow oil was formed at the bottom of the reaction flask. The reaction was monitored by TLC and when complete, the mixture was adjusted to pH 7 (5% $NaHCO_3$) and then extracted with DCM (x4). The organic phase was dried ($MgSO_4$) and DCM removed under reduced pressure to give a colourless crystalline solid. Purification by column chromatography using $CHCl_3$:MeOH (9:1) as eluent afforded analytical samples of **95β** and **98β**. Overall yield 964mg (83%).

8β-Bromocodide (98β)

Rf = 0.43 ($CHCl_3$:MeOH:NH_3 = 94:5:1); Mp. = 158°C (lit.[136] = 162°C); *m/z* (EI) 361.1 (M^++H, 15%), 282.1 (M^++H-Br, 100%); IR (Nujol) : 1635 (C=C), 1606 (ArC-C), 1504 (C-N), 1281 (ArC-O-CH_3), 1246 (C-O-C) cm^{-1}.

δ_H (270MHz) : 1.78 (1H, m, J_{gem} = 12.5Hz and $J_{15eq,16ax}$ = 3.7Hz, H-15_{eq}), 1.94 (1H, td, J_{gem} = 12.3Hz and $J_{15ax,16eq}$ = 5.1Hz, H-15_{ax}), 2.28 (1H, m, J_{gem} = 12.1Hz and $J_{16ax,15eq}$ = 3.7Hz, H-16_{ax}), 2.43 (1H, dd, J_{gem} = 18.7Hz and $J_{10\alpha,9}$ = 6.1Hz, H-10α), 2.45 (3H, s, N-$C\underline{H}_3$), 2.51 (1H, m, J_{gem} = 12.3Hz and $J_{16eq,15ax}$ = 5.1Hz, H-16_{eq}), 2.73 (1H, dd, $J_{14,8}$ = 9.9Hz and $J_{14,9}$ = 2.8Hz, H-14), 3.08 (1H, d, J_{gem} = 18.9Hz, H-10β), 3.57 (1H, dd, $J_{9,10\alpha}$ = 6.1Hz and $J_{9,14}$ = 2.8Hz, H-9), 3.84 (3H, s, O-$C\underline{H}_3$), 4.13 (1H, m, $J_{8,14}$ = 10.1Hz and $J_{8,7}$ = 1.5Hz, H-8), 5.04 (1H, d, $J_{5,6}$ = 3.3Hz, H-5), 5.69 (1H, m, $J_{6,7}$ =10.5Hz and $J_{6,5}$ = 3.3Hz, H-6), 6.05 (1H, dd, $J_{7,6}$ = 10.4Hz and $J_{7,8}$ = 1.5Hz, H-7), 6.65 (1H, d, $J_{1,2}$ = 8.2Hz, H-1), 6.72 (1H, d, $J_{2,1}$ = 8.2Hz, H-2).

δ_C (400MHz) : 19.50 (C-10), 35.21 (C-15), 42.75 (C-13), 43.11 (N-$\underline{C}H_3$), 46.64 (C-16), 47.08 (C-8), 49.18 (C-14), 56.32 (O-$\underline{C}H_3$), 56.99 (C-9), 86.36 (C-5), 113.45 (C-2), 119.19 (C-1), 125.63 (C-7), 126.76 (C-11), 128.37 (C-12), 135.30 (C-6), 143.33 (C-3), 143.99 (C-4).

Found : C, 59.3; H, 5.5; N, 3.8%, $C_{18}H_{20}NO_2Br$ requires C, 59.7; H, 5.6; N, 3.9%.

6β-Bromocodide (95β)

Rf = 0.30 ($CHCl_3$:MeOH:NH_3 = 94:5:1).

δ_H (270MHz) : 1.86 (1H, dd, J_{gem} = 12.3Hz, H-15_{eq}), 2.21 (1H, m, J_{gem} = 12.3Hz and $J_{15ax,16eq}$ = 4.9Hz, H-15_{ax}), 2.34 (1H, dd, J_{gem} = 18.5Hz and $J_{10\alpha,9}$ = 6.0Hz, H-10α), 2.41 (1H, m, J_{gem} = 12.3Hz, H-16_{ax}), 2.46 (3H, s, N-$C\underline{H}_3$), 2.62 (1H, dd, J_{gem} = 12.1Hz and $J_{16eq,15eq}$ = 3.8Hz, H-16_{eq}), 3.10 (1H, d, J_{gem} = 18.5Hz, H-

10β), 3.13 (1H, m, H-14), 3.40 (1H, dd, $J_{9,10\alpha}$ = 6.0Hz and $J_{9,14}$ = 3.3Hz, H-9), 3.84 (3H, s, O-C<u>H</u>3), 4.66 (1H, d, $J_{6,7}$ = 6.2Hz, H-6), 5.20 (1H, s, H-5), 5.64 (1H, dd, $J_{8,7}$ = 9.5Hz and $J_{8,14}$ = 2.0Hz, H-8), 6.03 (1H, m, $J_{7,8}$ = 9.3Hz, $J_{7,6}$ = 6.2Hz and $J_{7,14}$ = 2.9Hz, H-7), 6.58 (1H, d, $J_{1,2}$ = 8.3Hz, H-1), 6.67 (1H, d, $J_{2,1}$ = 8.3Hz, H-2).

δ_C (400MHz) : 20.46 (C-10), 29.70 (C-13), 36.34 (C-15), 39.96 (C-14), 43.09 (N-<u>C</u>H3), 44.71 (C-6), 46.67 (C-16), 56.35 (O-<u>C</u>H3), 58.67 (C-9), 93.80 (C-5), 112.97 (C-2), 119.29 (C-1), 127.38 (C-11), 129.48 (C-7), 130.01 (C-12), 135.37 (C-8), 141.88 (C-3), 145.83 (C-4).

Attempted coupling between 8β-bromocodide (98β) and allyltri-n-butyltin[72]

To a stirred solution of **98β** (97mg, 0.26mmol) in degassed toluene (0.25ml) under N_2 was added allyltri-*n*-butyltin (0.2ml, 0.5mmol) and AIBN (6mg, 0.15eq). The reaction temperature was raised to 80°C and the reaction monitored by TLC. After 6 hr, the complete disappearance of starting material was observed and the reaction mixture allowed to cool to room temperature. Attempted purification of the crude product by column chromatography on silica gel using CHCl3:MeOH (99:1) as eluent was unsuccessful. Analysis of the isolated fractions by mass spectrometry did not reveal the correct mass ion for the desired compound **96**.

Preparation of 6α-O-(thiocarbonylimidazole)codeine (116)

To a stirred solution of codeine (812mg, 2.7mmol) in DCM (20ml), at room temperature under nitrogen, was added N,N'-thiocarbonyldiimidazole[73] (967mg, 5.4mmol) portionwise. A colour change from colourless to yellow was observed. The reaction mixture was stirred at room temperature and monitored by TLC. After 8 hr, the reaction mixture was washed with sat. $NaHCO_3$ (x3), water, and then sat. NH_4Cl. The organic phase was dried ($MgSO_4$) and DCM evaporated off leaving a yellow oil. Purification by flash chromatography ($CHCl_3$:MeOH = 95:5) afforded a

yellow solid which after subsequent crystallisation from neat EtOAc gave the title compound as white crystalline plates. Yield 482mg (42%).

Rf = 0.43 ($CHCl_3$: MeOH = 9:1); Mp. = 156-157°C; *m/z* (FAB) : 410 (M^++H, 57%), 282 (M^++H - $C_4H_3N_2OS$, 100%); IR (Nujol) : 1639, 1607 (ArC-C), 1503 (C-N), 1398, 1348, 1313, 1279 (ArC-O-CH_3), 1240, 1214, 1109, 1003, 950, 799 cm^{-1}.

δ_H (270MHz) : 1.90 (1H, m, J_{gem} = 12.3Hz and $J_{15eq,16ax}$ = 3.8Hz, H-15_{eq}), 2.05 (1H, m, J_{gem} = 12.3Hz and $J_{15ax,16eq}$ = 4.9Hz, H-15_{ax}), 2.33 (1H, dd, J_{gem} = 18.7Hz and $J_{10\alpha,9}$ = 5.7Hz, H-10α), 2.37 (1H, m, J_{gem} = 12.1Hz and $J_{16ax,15eq}$ = 3.8Hz, H-16_{ax}), 2.45 (3H, s, N-C<u>H</u>$_3$), 2.62 (1H, m, J_{gem} = 12.1Hz and $J_{16eq,15ax}$ = 4.9Hz, H-16_{eq}), 2.82 (1H, m, H-14), 3.06 (1H, d, J_{gem} =18.7Hz, H-10β), 3.40 (1H, dd, $J_{9,10\alpha}$ = 5.7Hz and $J_{9,14}$ = 3.4Hz, H-9), 3.75 (3H, s, O-C<u>H</u>$_3$), 5.24 (1H, d, $J_{5,6}$ = 7.0Hz, H-5), 5.60 (1H, m, $J_{8,7}$ = 10.1Hz, H-8), 5.75 (1H, dm, $J_{7,8}$ =10.3Hz, H-7), 5.95 (1H, m, H-6), 6.60 (1H, d, $J_{1,2}$ = 8.3Hz, H-1), 6.68 (1H, d, $J_{2,1}$ = 8.3Hz, H-2), 7.03 (1H, q, Im-C<u>H</u>), 7.66 (1H, t, Im-C<u>H</u>), 8.32 (1H, s, Im-C<u>H</u>).

δ_C (400MHz) : 20.18 (C-10), 35.08 (C-15), 40.46 (C-14), 42.44 (N-<u>C</u>H$_3$), 42.98 (C-13), 46.70 (C-16), 56.23 (O-<u>C</u>H$_3$), 59.08 (C-9), 74.97 (C-6), 86.42 (C-5), 113.45 (C-2), 118.29 (C-Im), 119.63 (C-1), 126.69 (C-11), 126.73 (C-8), 130.24 (C-12), 130. 62 (C-7), 130.75 (C-Im), 136.89 (C-Im), 142.25 (C-3), 146.02 (C-4), 183.55 (C=S).

Found: C, 64.5%; H, 5.7%; N, 10.1%; $C_{22}H_{23}N_3O_3S$ requires C, 64.5%; H, 5.7%; N, 10.3%.

Attempted coupling of 116 with allyltri-n-butyltin

To a stirred solution of **116** (148mg, 0.4mmol) in degassed toluene (2ml) was added allyltri-*n*-butyltin (0.2ml, 0.7mmol) and AIBN (9mg, 0.15eq). The reaction temperature was raised to 80°C and the reaction monitored by TLC. The complete disappearance of starting material to at least 5 new components on TLC was observed

after 6 hr. After cooling, attempted purification of the crude mixture by column chromatography using $CHCl_3$:MeOH (95:5) as eluent proved unsuccessful. However, the mixed products were analysed by mass spectrometry but none of the fractions contained the desired compound **96**.

Dihydrocodeinone (117)

R_f = 0.40 ($CHCl_3$:MeOH:NH_3 = 90:9:1); Mp. = 195-196°C; IR (Nujol) : 1716 (C=O), 1607 (ArC-C), 1500 (C-N), 1270 (ArC-O-CH_3), 1180 (C-O-C) cm^{-1}.

δ_H (270MHz) : 1.26 (1H, m, H-8_{eq}), 1.78-1.90 (2H, m, H-8_{ax} and H-15_{eq}), 2.06 (1H, m, J_{gem} = 11.9Hz and $J_{15ax,16eq}$ = 4.4Hz, H-15_{ax}), 2.19 (1H, m, J_{gem} = 12.0Hz and $J_{16ax,15eq}$ = 3.5Hz, H-16_{ax}), 2.31 (1H, dd, J_{gem} = 18.7Hz and $J_{10\alpha,9}$ = 5.7Hz, H-10α), 2.31-2.46 (2H, m, H-7_{ax} and H-7_{eq}), 2.43 (3H, s, N-C<u>H</u>3), 2.53-2.60 (2H, m, H-14 and H-16_{eq}), 3.04 (1H, d, J_{gem} = 18.7Hz, H-10β), 3.19 (1H, dd, $J_{9,10\alpha}$ = 5.4Hz and $J_{9,14}$ = 2.8Hz, H-9), 3.90 (3H, s, O-C<u>H</u>3), 4.66 (1H, s, H-5), 6.64 (1H, d, $J_{1,2}$ = 8.2Hz, H-1), 6.70 (1H, d, $J_{2,1}$ = 8.2Hz, H-2).

δ_C (400MHz) : 19.48 (C-10), 25.08 (C-8), 34.97 (C-15), 39.69 (C-7), 42.07 (C-14), 42.44 (N-<u>C</u>H3), 46.31 (C-16), 46.38 (C-13), 56.24 (O-<u>C</u>H3), 58.64 (C-9), 90.90 (C-5), 114.05 (C-2), 119.28 (C-1), 125.90 (C-11), 126.85 (C-12), 142.23 (C-3), 144.89 (C-4), 207.43 (C-6).

Reduction of 117

(a) with sodium borohydride[74]

To a cooled (ice bath) solution of **117** (50mg, 0.16mmol) in methanol (5ml) was added sodium borohydride (13mg, 0.33mmol) portionwise. The mixture was then allowed to stir at room temperature. When the reaction was complete (by TLC) the mixture was concentrated to half its original volume, washed with 10% NaOH (25ml),

water (10ml) and at d3 (x4). The organic phase was dried ($MgSO_4$), and chloroform evaporated under reduced pressure leaving a colourless oil. Column chromatography on silica gel ($CHCl_3$:MeOH:NH_3 = 90:9:1) afforded a mixture of **118α** and **118β** in the ratio 4.5:1 respectively. Overall yield 47mg (94%).

(b) with diisobutylaluminium hydride [75]

To a stirred solution of **117** (60mg, 0.2mmol) in dry THF (5ml) at -78°C was added diisobutylaluminium hydride (0.3ml, 0.4mmol) dropwise. After 1 hr, TLC analysis showed the absence of starting material and the reaction was quenched with Rochelle salts. The product was extracted with DCM (x3), dried ($MgSO_4$) and solvent evaporated under reduced pressure. The colourless oil was triturated with ether to afford **118α** as a colourless powder (45mg, 75%).

(c) with K-selectride [76]

To a stirred solution of **117** (61mg, 0.2mmol) in THF (5ml) at -78°C was added K-Selectride (0.4ml, 0.4mmol) dropwise. The reaction was followed by TLC and when complete (1 hr) quenched with water. The product was extracted with DCM (x3), dried ($MgSO_4$) and solvent evaporated off leaving a yellow oil. Trituration with EtOAc gave **118α** as a colourless powder (42mg, 68%).

6α-Dihydrocodeine (118α)

R_f = 0.36 ($CHCl_3$:MeOH:NH_3 = 18:1:1); Mp. = 111-112°C (lit.[136] = 112-113°C); *m/z* (FAB) : 302.2 (M^++H, 92%); IR (neat) = 3119 (OH), 1602 (ArC-C), 1503 (C-N), 1275 (ArC-O-CH_3), 1205 (C-O-C) cm^{-1}.

δ_H (270MHz) : 1.16 (1H, m, H-8α), 1.42 (1H, m, H-8β), 1.47 (1H, m, H-7α), 1.57 (1H, m, H-7β), 1.70 (1H, m, J_{gem} = 12.2Hz, and $J_{15eq,16ax}$ = 3.9Hz, H-15_{eq}), 1.88 (1H, td, J_{gem} = 12.2Hz, J_{diax} = 12.2Hz and $J_{15ax,16eq}$ = 4.9Hz, H-15_{ax}), 2.08 (1H,

br. s, OH), 2.21 (1H, m, $J_{14,9}$ = 2.7Hz, H-14), 2.25 (1H, td, J_{gem} = 12.2Hz, J_{diax} = 12.2Hz and, $J_{16ax,15eq}$ = 3.9Hz, H-16_{ax}), 2.38 (1H, dd, J_{gem} = 18.4Hz, and $J_{10\alpha,9}$ = 5.7Hz, H-10α), 2.40 (3H, s, N-C<u>H</u>3), 2.51 (1H, m, J_{gem} = 12.1Hz and $J_{16,15ax}$ = 4.9Hz, H-16_{eq}), 3.00 (1H, d, J_{gem} = 18.4Hz, H-10β), 3.08 (1H, dd, $J_{9,10\alpha}$ = 5.7Hz and $J_{9,14}$ = 2.7Hz, H-9), 3.87 (3H, s, O-C<u>H</u>3), 4.04 (1H, m, $J_{6,5}$ = 5.3Hz, H-6), 4.61 (1H, d, $J_{5,6}$ = 5.3Hz, H-5), 6.63 (1H, d, $J_{1,2}$ = 7.2Hz, H-1), 6.68 (1H, d, $J_{2,1}$ = 7.2Hz, H-2).

δ_C (400MHz): 19.08 (C-10), 19.96 (C-8), 27.17 (C-7), 37.37 (C-15), 40.66 (C-14), 42.13 (C-13), 42.98 (N-Me), 46.79 (C-16), 56.30 (O-Me), 59.68 (C-9), 67.16 (C-6), 90.42 (C-5), 113.05 (C-2), 119.14 (C-1), 126.91 (C-11), 130.27 (C-12), 141.54 (C-3), 146.11 (C-4).

Found: C, 71.5%; H, 7.8%; N, 4.6%; $C_{18}H_{23}NO_3$ requires C, 71.7%; H, 7.7%; N, 4.7%.

6β-Dihydrocodeine (118β)

R_f = 0.18 ($CHCl_3$:MeOH:NH_3 = 18:1:1); *m/z* (FAB) = 302.2 (M^++H, 100%)

δ_H (270MHz) : 0.97 (1H, m, J_{gem} = 13.0, $J_{8ax,7ax}$ = 12.8Hz, $J_{8ax,7eq}$ = 2.6Hz, H-8_{ax}), 1.37 (1H, dq, $J_{7ax,8ax}$ = 12.8Hz, J_{gem} = 12.6Hz, $J_{7ax,8eq}$ = 3.0Hz, H-7_{ax}), 1.52-1.62 (1H, m, H-8_{eq}), 1.69 (1H, ddd, J_{gem} = 12.3Hz, and $J_{15eq,16ax}$ = 3.7Hz, H-15_{eq}), 1.79 (1H, m, J_{gem} = 12.6, $J_{7eq,6}$ = 6.6Hz, H-7_{eq}), 1.86 (1H, m, J_{gem} = 12.3Hz, and $J_{15ax,16eq}$ = 5.0Hz, H-15_{ax}), 2.13-2.21 (1H, m, H-14), 2.14 (1H, m, J_{gem} = 11.9Hz and $J_{16ax,15eq}$ = 3.7Hz, H-16_{ax}), 2.35 (1H, dd, J_{gem} = 18.3Hz, and $J_{10\alpha,9}$ = 5.3Hz, H-10α), 2.40 (3H, s, N-C<u>H</u>3), 2.54 (1H, dd, J_{gem} = 11.9Hz and $J_{16,15ax}$ = 4.4Hz, H-16_{eq}), 3.01 (1H, d, J_{gem} = 18.5Hz, H-10β), 3.12 (1H, dd, $J_{9,10\alpha}$ = 5.3Hz, H-9), 3.42 (1H, ddd, $J_{6,7ax}$ = 12.3Hz, $J_{6,7eq}$ = 6.6Hz and $J_{6,5}$ = 6.4Hz, H-6), 3.85 (3H, s, O-C<u>H</u>3), 4.38 (1H, d, $J_{5,6}$ = 6.4Hz, H-5), 6.63 (1H, d, $J_{1,2}$ = 8.2Hz, H-1), 6.71 (1H, d, $J_{2,1}$ = 8.3Hz, H-2).

δ_C (400MHz): 20.08 (C-10), 23.72 (C-8), 30.19 (C-7), 35.44 (C-15), 42.76 (C-14 and N-CH_3), 43.12 (C-13), 46.98 (C-16), 56.40 (O-CH_3), 59.31 (C-9), 72.97 (C-6), 97.31 (C-5), 113.29 (C-2), 118.89 (C-1), 126.57 (C-11), 130.58 (C-12), 143.49 (C-3), 144.11 (C-4).

HRMS (FAB) : found 302.1756, $C_{18}H_{24}NO_3$ (M^++H) requires 302.1756.

Bromination of 118α

a) with phosphorus tribromide[69]

To a stirred solution of **118α** (738mg, 2.5mmol) in distilled DCM (5ml) at room temperature was added PBr_3 (0.35ml, 3.7mmol). When the reaction was complete, (by TLC) the mixture was adjusted to pH 7 (sat. $NaHCO_3$) and the product extracted with DCM (x4). After drying ($MgSO_4$), the organic phase was filtered and DCM evaporated to dryness to give **119β** as a colourless crystalline solid. Yield 460mg (52%).

b) with N-bromosuccinimide[95]

To a stirred solution of **118α** (170mg, 0.56mmol) in DCM was added triphenylphosphine (163mg, 0.6mmol) and *N*-bromosuccinimide (111mg, 0.6mmol). The mixture was stirred at room temperature and the reaction followed by TLC. After 24 hr, no reaction was observed and the starting material was recovered quantitatively.

6β-Bromodihydrocodide (119β)

Rf = 0.61 ($CHCl_3$:MeOH:NH_3 = 90:10:1); Mp. = 158-159°C; *m/z* : CI 364.0 (M^++H, 32%), 284.1 (M^++H - Br, 100%); IR (Nujol) = 1633, 1609 (ArC-C), 1500 (C-N), 1344, 1321, 1273 (ArC-O-CH_3), 1184, 1148, 1100, 1055, 937, 909, 799 cm^{-1}.

δ_H (270MHz) : 1.01 (1H, m, J_{gem} = 12.8Hz, H-8α), 1.58 (1H, m, H-8β), 1.70 (1H, m, J_{gem} = 12.1Hz, and $J_{15eq,16ax}$ = 3.7Hz, H-15$_{eq}$), 1.83 (1H, dm, H-7α), 1.86 (1H, m, J_{gem} = 12.1Hz, and $J_{15ax,16eq}$ = 4.6Hz, H-15$_{ax}$), 2.13 (1H, m, $J_{14,9}$ = 2.9Hz, H-14), 2.14 (1H, m, J_{gem} = 11.9Hz and $J_{16ax,15eq}$ = 3.7Hz, H-16$_{ax}$), 2.27 (1H, m, H-7β), 2.33 (1H, dd, J_{gem} = 18.7Hz, and $J_{10\alpha,9}$ = 5.3Hz, H-10α), 2.39 (3H, s, N-CH3), 2.52 (1H, m, J_{gem} = 11.9Hz and $J_{16,15ax}$ = 4.6Hz, H-16$_{eq}$), 3.01 (1H, d, J_{gem} = 18.5Hz, H-10β), 3.07 (1H, dd, $J_{9,10\alpha}$ = 5.3Hz and $J_{9,14}$ = 2.9Hz, H-9), 3.75 (1H, ddd, $J_{6,7diax}$ = 13.0Hz, $J_{6,5}$ = 7.5Hz and $J_{6,7eq}$ = 4.6Hz, H-6), 3.90 (3H, s, O-CH3), 4.70 (1H, d, $J_{5,6}$ = 7.5Hz, H-5), 6.67 (1H, d, $J_{1,2}$ = 8.2Hz, H-1), 6.68 (1H, d, $J_{2,1}$ = 8.1Hz, H-2).

δ_C (400MHz): 19.99 (C-10), 26.10 (C-8), 33.80 (C-7), 35.68 (C-15), 42.36 (C-14), 42.89 (N-CH3), 43.18 (C-13), 47.07 (C-16), 52.65 (C-6), 56.88 (O-CH3), 59.31 (C-9), 95.98 (C-5), 114.48 (C-2), 119.42 (C-1), 126.85 (C-11), 129.39 (C-12), 143.67 (C-3), 143.93 (C-4).

Found: C, 60.5; H, 6.2; N, 3.9%; $C_{18}H_{22}NO_2Br$ requires: C, 59.4; H, 6.1; N, 3.8%.

Attempted coupling between 119β and allyltri-n-butyltin[72]

To a stirred solution of **119β** (136mg, 0.4mmol) in degassed toluene (0.4ml) under N_2 was added allyltri-*n*-butyltin (0.2ml, 0.75mmol) and AIBN (9mg, 0.006mmol). The reaction temperature was raised to 80°C and the reaction left stirring for 8 hr. Attempted purification of the crude reaction mixture by column chromatography using CHCl3:MeOH:NH3 (90:9:1) as eluent was unsuccessful and mass spectrometric analysis of the mixed fractions did not reveal the appropriate mass ion for the desired compound **96**.

Radical coupling between 119β and tri-n-butyltinhydride

To a stirred solution of **119β** (212mg, 0.6mmol) in degassed toluene (2.5ml) under N_2 was added tri-*n*-butyltinhydride (0.2ml, 0.7mmol). The reaction temperature was raised to 80°C and a catalytic amount of AIBN added. A further amount of AIBN was added after 1 hr and the disappearance of starting material was monitored by TLC. After 3 hr, the reaction mixture was cooled to room temperature, toluene removed *in vacuo* and the resultant residue dissolved in EtOAc. The organic layer was washed (x2) with a 10% aqueous solution of tartaric acid, the combined aqueous extracts made alkaline (pH 9) with conc. NH_4OH and then extracted with chloroform (x3). The combined chloroform layers were dried ($MgSO_4$) and removal of solvent afforded a 1:1 mixture of **122** and **123** as a colourless oil. Attempted separation of the two compounds by column chromatography was unsuccessful. Total yield 95mg.

Dihydrodeoxycodeine-D (122)

Rf = 0.43 ($CHCl_3$:MeOH = 9:1); *m/z* (FAB) = 286.1 (M^++H, 99%).

δ_H (400MHz) : 1.17-1.28 (2H, m, H-6 and H-7), 1.52-1.61 (2H, m, H-7 and H-8), 1.77-1.84 (1H, m, H-15_{eq}), 1.87-1.97 (2H, m, H-8 and H-15_{ax}), 2.12-2.18 (1H, m, H-6), 2.28 (1H, m, J_{gem} = 12.2Hz and $J_{16ax,15eq}$ = 3.9Hz, H-16_{ax}), 2.36 (1H, dd, J_{gem} = 18.1Hz, and $J_{10\alpha,9}$ = 5.4Hz, H-10α), 2.38-2.45 (1H, m, H-14), 2.41 (3H, s, N-$C\underline{H}_3$), 2.49-2.56 (1H, m, H-16_{eq}), 3.01 (1H, d, J_{gem} = 18.1Hz, H-10β), 3.11 (1H, dd, $J_{9,10\alpha}$ = 5.9Hz and $J_{9,14}$ = 2.9Hz, H-9), 3.85 (3H, s, O-$C\underline{H}_3$), 4.60 (1H, t, $J_{5,6}$ = 8.0Hz, H-5), 6.63 (1H, d, $J_{1,2}$ = 8.3Hz, H-1), 6.72 (1H, d, $J_{2,1}$ = 8.3Hz, H-2).

δ_C (400MHz): 19.96 (C-10), 21.53 (C-7), 24.29 (C-8), 29.18 (C-6), 35.43 (C-15), 38.87 (C-14), 40.64 (C-13), 42.78 (N-CH_3), 47.48 (C-16), 56.26 (O-CH_3), 59.63 (C-9), 89.49 (C-5), 112.87 (C-2), 118.42 (C-1), 127.09 (C-11), 130.16 (C-12), 143.42 (C-3), 144.59 (C-4).

HRMS (FAB) : found 286.1809, $C_{18}H_{24}NO_2$ (M^++H) requires 286.1809.

Deoxycodeine-C (123)

Rf = 0.43 ($CHCl_3$:MeOH = 9:1); *m/z* (FAB) = 284.1 (M^++H, 100%).

δ_H (400MHz) : 0.83-0.95 (1H, m, H-8), 1.45-1.52 (1H, m, H-8), 1.66-1.73 (1H, m, H-15_{eq}), 1.79 (2H, m, J_{gem} = 12.2Hz and $J_{15ax,16}$ = 4.9Hz, H-15_{ax}), 2.08-2.20 (1H, m, H-14), 2.19 (1H, m, J_{gem} = 12.2Hz and $J_{16ax,15eq}$ = 3.9Hz, H-16_{ax}), 2.36 (1H, dd, J_{gem} = 18.1Hz, and $J_{10\alpha,9}$ = 5.4Hz, H-10_{α}), 2.39 (3H, s, N-$C\underline{H}_3$), 2.49-2.56 (1H, m, H-16_{eq}), 3.02 (1H, d, J_{gem} = 18.1Hz, H-10_{β}), 3.11 (1H, dd, $J_{9,10\alpha}$ = 5.9Hz and $J_{9,14}$ = 2.9Hz, H-9), 3.84 (3H, s, O-$C\underline{H}_3$), 4.95 (1H, s, H-5), 5.70 (1H, m, $J_{7,6}$ = 10.3Hz and $J_{7,8}$ = 3.5Hz, H-7), 5.84 (1H, ddd, J = 10.3Hz, J = 5.9Hz and J = 1.95Hz, H-6), 6.61 (1H, d, $J_{1,2}$ = 8.3Hz, H-1), 6.70 (1H, d, $J_{2,1}$ = 8.3Hz, H-2).

δ_C (400MHz): 19.76 (C-10), 24.86 (C-8), 35.47 (C-15), 42.31 (C-13), 43.02 (N-CH_3), 43.17 (C-14), 46.35 (C-16), 56.13 (O-CH_3), 59.01 (C-9), 87.55 (C-5), 112.72 (C-2), 118.37 (C-1), 124.53 (C-6), 127.09 (C-11), 129.51 (C-12), 132.01 (C-7), 143.08 (C-3), 143.95 (C-4).

HRMS (FAB) : found 284.1657, $C_{18}H_{21}NO_2$ (M^++H) requires 284.1650.

Preparation of 6-(methylidenyl)dihydrodeoxycodeine[79] (125)

To a stirred, cooled (waterbath at 20°C) suspension of methyltriphenylphosphonium bromide (50) (1.19g, 3.34mmol) in THF (20ml) was added potassium *tert*-butoxide (0.36g, 3.21mmol) in one portion. After 1 hr, **117** (0.50g, 1.67mmol) was added to the bright yellow ylide solution. The mixture was stirred for a 1 hr at 20°C, heated at reflux for 7 hr and then stirred overnight at room temperature. THF was removed *in vacuo* and the residue dissolved in DCM and washed with water (x3). The aqueous layer was re-extracted with DCM and the combined organic extracts were dried

($MgSO_4$) and solvent removed under reduced pressure. Purification by column chromatography on silica gel using $CHCl_3$:MeOH: (9:1) afforded the title compound as a colourless solid (0.34g, 71%).

R_f = 0.52 ($CHCl_3$:MeOH = 9:1); Mp. = 123-125°C (lit.[79] = 127-129°C); *m/z* (FAB) = 298.2 (M^++H, 100%); IR (Nujol) = 1633 (C=C), 1609 (ArC-C), 1500 (C-N), 1271 (ArC-O-CH_3) cm^{-1}.

δ_H (270MHz) : 0.94 (1H, m, J_{gem} = 12.8Hz and $J_{8ax,7eq}$ = 2.9Hz, H-8_{ax}), 1.58 (1H, m, J_{gem} = 12.8Hz, H-8_{eq}), 1.75 (1H, m, J_{gem} = 12.1Hz, H-15_{eq}), 1.92 (1H, m, J_{gem} = 12.1Hz and $J_{15ax,16eq}$ = 4.6Hz, H-15_{ax}), 1.97-2.06 (1H, m, H-7), 2.20 (1H, m, J_{gem} = 12.0Hz, $J_{16ax,15eq}$ = 3.7Hz, H-16_{ax}), 2.23-2.39 (2H, m, H-14 and H-7), 2.32 (1H, dd, J_{gem} = 18.5Hz and $J_{10\alpha,9}$ = 4.8Hz, H-10α), 2.41 (3H, s, N-C<u>H</u>$_3$), 2.56 (1H, dd, J_{gem} = 12.0Hz and $J_{16eq,15ax}$ = 4.4Hz, H-16_{eq}), 2.99 (1H, d, J_{gem} = 18.5Hz, H-10β), 3.09 (1H, dd, $J_{9,10\alpha}$ = 4.8Hz and $J_{9,14}$ = 3.0Hz, H-9), 3.87 (3H, s, O-C<u>H</u>$_3$), 4.81 (1H, s, *cis* =C<u>H</u>), 4.91 (1H, s, H-5), 5.27 (1H, s, *trans* =C<u>H</u>), 6.60 (1H, d, $J_{1,2}$ = 8.2Hz, H-1), 6.70 (1H, d, $J_{2,1}$ = 8.2Hz, H-2).

δ_C (400MHz): 19.83 (C-10), 26.11 (C-8), 32.23 (C-7), 35.03 (C-15), 42.55 (N-<u>C</u>H$_3$), 42.98 (C-14), 43.97 (C-13), 47.28 (C-16), 56.43 (O-<u>C</u>H$_3$), 59.48 (C-9), 89.66 (C-5), 110.74 (=<u>C</u>H$_2$), 113.59 (C-2), 118.62 (C-1), 126.51 (C-11), 128.99 (C-12), 142.75 (C-3), 144.72 (C-4), 145.25 (C-6).

Found: C, 76.5; H, 7.9; N, 4.65%. $C_{19}H_{23}NO_2$ requires: C, 76.7; H, 7.8; N, 4.7%.

Attempted coupling between 125 and cyclohexyl bromide [78]

A mixture of **125** (153mg, 0.52mmol), tri-*n*-butyltin hydride (0.15ml, 0.56mmol) and cyclohexyl bromide (0.06ml, 0.49mmol) in toluene (2ml) was heated to 80°C before AIBN (catalytic) was added. The reaction was followed by TLC and a further three

portions of AIBN added after 45, 120 and 180 min. After 4 hr TLC analysis showed no reaction and the starting material was recovered.

Preparation of 6-(methoxymethylidenyl)dihydrodeoxycodeine [82] ***(141)***

To a stirred suspension of methoxymethyltriphenylphosphonium bromide (1.15g, 3.34mmol) in THF (14ml), maintained at 20°C was added potassium *tert*-butoxide (0.37g, 3.34mmol) in one portion. After 1 hr, **117** (0.5g, 1.67mmol) was added to the deep red ylide solution. The mixture was stirred for 1 hr at 20°C, heated at reflux for 11 hr and then stirred overnight at room temperature. THF was removed *in vacuo* and the residue diluted with water and extracted with DCM (x3). The organic extracts were dried ($MgSO_4$) and solvent removed under reduced pressure. Purification by column chromatography on silica gel using $CHCl_3$:MeOH (95:5) as eluent afforded the product as a mixture of *E*:*Z* isomers in the ratio 2.5:1 respectively. Overall Yield 0.56g (51%).

(E)-141

R_f = 0. 43 ($CHCl_3$:MeOH = 9:1); *m/z* (FAB) : 328.2 (M^++H, 100%); IR (neat) = 1675 (C=CHOMe), 1633 (C=C), 1604 (ArC-C), 1502 (C-N) cm^{-1}

δ_H (270MHz) : 0.80-1.00 (1H, m, H-7), 1.45-1.55 (1H, m, H-7), 1.72 (1H, dd, J_{gem} = 11.7Hz, H-15_{eq}), 1.76-1.90 (2H, m, H-8_{ax} and H-8_{eq}), 1.93 (1H, m; J_{gem} = 11.7Hz and $J_{15ax,16eq}$ = 5.2Hz, H-15_{ax}), 2.12-2.35 (2H, m, H-16_{ax} and H-14), 2.37 (1H, dd, J_{gem} = 18.5Hz and $J_{10\alpha,9}$ = 5.9Hz, H-10α), 2.41 (3H, s, N-C<u>H</u>$_3$), 2.53 (1H, dd, J_{gem} = 11.6Hz and $J_{16eq,15eq}$ = 5.2Hz, H-16_{eq}), 2.98 (1H, d, J_{gem} = 18.5Hz, H-10β), 3.09 (1H, dd, $J_{9,10\alpha}$ = 5.9Hz and $J_{9,14}$ = 2.7Hz, H-9), 3.61 (3H, s, C^6=C^{19}H-O-C<u>H</u>$_3$), 3.83 (3H, s, ArC-O-C<u>H</u>$_3$), 5.37 (1H, d, $J_{5,19}$ = 1.2Hz, H-5), 5.86 (1H, d, $J_{19,5}$ = 1.2Hz, C^6=C^{19}<u>H</u>-O-CH_3), 6.58 (1H, d, $J_{1,2}$ = 8.1Hz, H-1), 6.70 (1H, d, $J_{2,1}$ = 8.1Hz, H-2).

δ_C (400MHz): 20.21 (C-10), 22.67 (C-8), 22.97 (C-7), 35.36 (C-15), 39.48 (C-14), 42.07 (C-13), 42.81 (N-$\underline{C}H_3$), 46.89 (C-16), 56.77 (ArC-O-$\underline{C}H_3$), 59.71 (C^6=C^{19}H-O-$\underline{C}H_3$), 60.06 (C-9), 87.11 (C-5), 111.74 (C-6), 114.06 (C-2), 118.27 (C-1), 127.21 (C-11), 129.94 (C-12), 142.23 (C-3), 144.86 (C-4), 146.19 (C^6=$\underline{C}^{19}$H-O-CH_3).

HRMS (FAB) : found 328.1929, $C_{20}H_{26}NO_3$ (M^++H) requires 328.1913.

(Z)-141

δ_H (270MHz) includes : 3.53 (3H, s, C^6=$C^{19}\underline{H}$-O-CH_3), 4.96 (1H, s, H-5), 6.29 (1H, s, C^6=$C\underline{H}$-O-CH_3).

δ_C (400MHz) includes : 89.37 (C-5), 113.18 (C-6), 145.26 (C^6=$\underline{C}^{19}$H-O-CH_3).

Dehydration of 141 using p-toluene sulfonic acid

A mixture of *p*-toluene sulfonic acid (49mg, 0.24mmol), water (4ml), 1,4-dioxane (10ml) and **141** (390mg, 1.19mmol) was heated at reflux for 16 hr. The cooled mixture was adjusted to pH 9 by the addition of NH_4OH and extracted with DCM (x3). The combined organic extracts were dried ($MgSO_4$) and solvent removed under reduced pressure. Crystallisation of the resultant white solid from diethyl ether yielded pure **143** (285mg, 76%).

6-Formyl-4-hydroxy-3-methoxy-N-methylmorphinan-5-ene (143)

R_f = 0.30 ($CHCl_3$:MeOH:NH_3 = 90:9:1); Mp. = 177-178°C; *m/z* (FAB) : 314.2 (M^++H, 100%); IR (Nujol) = 3189 (OH), 2810, 2715 (CHO), 1676 (C=O), 1631 (C=C), 1606 (ArC-C), 1580, 1274 (ArC-O-CH_3) cm^{-1}.

δ_H (270MHz) : 1.52 (1H, m, H-8_{ax}), 1.59-171 (1H, m, H-8_{eq}), 1.78 (1H, m, J_{gem} = 11.4Hz and $J_{15ax,16eq}$ = 4.7Hz, H-15_{ax}), 1.90 (1H, br. d, $J_{14,8ax}$ = 12.6Hz, H-14), 2.04 (1H, dd, J_{gem} = 11.4Hz and $J_{15eq,16eq}$ = 3.0Hz, H-15_{eq}), 2.10-2.30 (2H, m, H-

16_{ax} and H-7_{eq}), 2.31 (1H, br. d, J_{gem} = 18.2Hz and $J_{7ax,8eq}$ = 6.7Hz, H-7_{ax}), 2.40 (3H, s, N-C$\underline{H}_3$), 2.58 (1H, m, J_{gem} = 11.9Hz and $J_{16eq,15eq}$ = 3.0Hz, H-16_{eq}), 2.69 (1H, dd, J_{gem} = 18.3Hz and $J_{10\alpha,9}$ = 5.5Hz, H-10α), 3.00 (1H, d, $J_{9,10\alpha}$ = 5.5Hz, H-9), 3.01 (1H, d, J_{gem} = 18.3Hz, H-10β), 3.83 (3H, s, O-C$\underline{H}_3$), 6.63 (1H, d, $J_{1,2}$ = 8.2Hz, H-1), 6.70 (1H, d, $J_{2,1}$ = 8.2Hz, H-2), 7.69 (1H, s, H-5), 9.55 (1H, s, C$\underline{H}$O).

δ_C (400MHz): 21.77 (C-7), 22.74 (C-8), 23.36 (C-10), 35.67 (C-15), 38.61 (C-13), 42.38 (N-$\underline{C}H_3$), 43.06 (C-14), 47.50 (C-16), 55.88 (O-$\underline{C}H_3$), 57.43 (C-9), 108.75 (C-2), 118.72 (C-1), 125.12 (C-11), 129.30 (C-12), 138.48 (C-6), 143.77 (C-3), 144.85 (C-4), 158.55 (C-5), 195.60 (C=O).

HRMS (FAB) : found 314.1756, $C_{19}H_{24}NO_3$ (M^++H) requires 314.1772.

Preparation of cyclohexylmethyltriphenylphosphonium bromide*[83] *(139)

A mixture of triphenylphosphine (10g, 38mmol) and cyclohexylmethyl bromide (5.32ml, 38mmol) in toluene (20ml) were heated at reflux for 28 hr. After cooling, the resultant solid was collected and then washed with toluene to afford the title compound as a colourless powder (4.28g, 26%).

Mp. = 230-232°C (lit.[83] = 230-233°C); *m/z* (FAB) = 359.2 (M^+-Br, 100%); IR (Nujol) = 1115, 994, 893, 814, 793, 746, 723, 691 cm^{-1}.

δ_H (270MHz) : 0.96-1.68 (11H, m, $C_6\underline{H}_{11}$), 3.96 (2H, dd, J_{gem} = 12.9Hz and J = 6.0Hz, C_6H_{11}-C$\underline{H}_2$-PPh_3), 7.67-7.94 (15H, m, $(C_6\underline{H}_5)_3$).

δ_C (400MHz) : 25.11, 25.92, 28.92, 29.39 and 34.44 (CH_2), 33.49 (CH), 34.54 (CH_2-bridge), 118.51, 119.35, 129.71, 129.82, 130.33, 130.46, 130.69, 133.29, 133.47, 133.58, 133.86, 133.99, 134.86 and 134.90 (ArCH).

HRMS (FAB) : found 359.1929, $C_{25}H_{28}P$ (M^+ - Br) requires 359.1929.

Preparation of 6-(cyclohexylmethylidenyl)dihydrodeoxycodeine (138)

To a stirred, cooled (waterbath at 20°C) suspension of **139** (1.19g, 3.34mmol) in THF (28ml) was added potassium *tert*-butoxide (0.37g, 3.34mmol) in one portion. After 90 min, **117** (0.50g, 1.67mmol) was added to the deep orange ylide solution. The mixture was stirred for 15 min at 20°C, heated at reflux for 6 hr and then stirred overnight at room temperature. THF was removed *in vacuo* and the residue dissolved in DCM and washed with water (x3). The organic extract was dried ($MgSO_4$) and solvent removed under reduced pressure. Purification of the resultant residue by column chromatography on silica gel using $CHCl_3$:MeOH (9:1) as eluent afforded the title compound as a 1:1 mixture of *E/Z* isomers. Overall yield 0.58g (91%).

(Z)-138

R_f = 0.49 ($CHCl_3$:MeOH:NH_3 = 95:5:1); *m/z* (FAB) : 380.2 (M^++H, 100%); IR (Nujol) = 1636 (C=C), 1607 (ArC-C), 1503 (C-N), 1275 (ArC-O-CH_3) cm^{-1}.

δ_H (400MHz) : 0.89-1.03 (3H, m, H-8 and C$\underline{H}_2$-cyclohexyl), 1.09-1.18 (1H, m, C$\underline{H}_2$-cyclohexyl), 1.29-1.43 (3H, m, C$\underline{H}_2$-cyclohexyl), 1.45-1.52 (1H, m, H-8), 1.61-1.76 (6H, m, H-15_{eq} and C$\underline{H}_2$-cyclohexyl), 1.89 (1H, m, J_{gem} = 12.2Hz and $J_{15ax,16eq}$ = 4.9Hz, H-15_{ax}), 2.00-2.03 (2H, m, H-7_{ax} and H-7_{eq}), 2.13-2.19 (1H, m, H-14), 2.14 (1H, td, J_{gem} = 12.2Hz, $J_{16ax,15eq}$ = 3.4Hz, H-16_{ax}), 2.34 (1H, dd, J_{gem} = 18.6Hz and $J_{10\alpha,9}$ = 5.9Hz, H-10α), 2.40 (3H, s, N-C$\underline{H}_3$), 2.51 (1H, dd, J_{gem} = 12.2Hz and $J_{16eq,15ax}$ = 3.9Hz, H-16_{eq}), 2.68-2.78 (1H, m, C$\underline{H}$-cyclohexyl), 2.98 (1H, d, J_{gem} = 18.6Hz, H-10β), 3.07 (1H, dd, $J_{9,10\alpha}$ = 5.9Hz and $J_{9,14}$ = 2.9Hz, H-9), 3.84 (3H, s, O-C$\underline{H}_3$), 5.11 (1H, d, *J* = 9.8Hz, C^6=C$\underline{H}$-cyclohexyl), 5.20 (1H, d, *J* = 1.5Hz, H-5), 6.59 (1H, d, $J_{1,2}$ = 8.3Hz, H-1), 6.70 (1H, d, $J_{2,1}$ = 8.3Hz, H-2).

δ_C (400MHz): 20.03 (C-10), 24.62 (C-8), 25.84, 25.93 and 26.17 (C$\underline{H}_2$-cyclohexyl), 31.69 (C-7), 33.41 and 33.69 (C$\underline{H}_2$-cyclohexyl), 36.49 (C-15), 37.29 (C$\underline{H}$-cyclohexyl), 41.57 (C-14), 43.00 (N-C$\underline{H}_3$), 43.86 (C-13), 47.09 (C-16), 56.40 (O-

$\underline{C}H_3$), 59.88 (C-9), 89.63 (C-5), 113.29 (C-2), 118.38 (C-1), 127.32 (C-11), 129.90 (C-12), 131.75 (C-6), 137.86 (C^6=$\underline{C}$H-cyclohexyl), 142.43 (C-3), 145.63 (C-4).

HRMS (FAB) : found 380.2608, $C_{25}H_{34}NO_2$ (M^++H) requires 380.2590.

(E)-138

R_f = 0.42 ($CHCl_3$:MeOH:NH_3 = 95:5:1).

δ_H (400MHz) : 0.77-1.00 (2H, m, C$\underline{H}_2$-cyclohexyl), 1.03-1.40 (4H, m, C$\underline{H}_2$-cyclohexyl), 1.52-1.76 (8H, m, H-7_{ax}, H-7_{eq}, H-8, H-15_{eq} and C$\underline{H}_2$-cyclohexyl), 1.88 (1H, m, J_{gem} = 12.2Hz and $J_{15ax,16eq}$ = 4.9Hz, H-15_{ax}), 2.01-2.13 (1H, m, C$\underline{H}$-cyclohexyl), 2.17 (1H, m, J_{gem} = 12.2Hz, $J_{16ax,15eq}$ = 3.4Hz, H-16_{ax}), 2.20-2.27 (1H, m, H-14), 2.30 (1H, dd, J_{gem} = 18.6Hz and $J_{10\alpha,9}$ = 5.4Hz, H-10α), 2.38-2.44 (1H, m, H-8), 2.40 (3H, s, N-$\underline{C}H_3$), 2.53 (1H, dd, J_{gem} = 12.2Hz and $J_{16eq,15ax}$ = 3.4Hz, H-16_{eq}), 2.97 (1H, d, J_{gem} = 18.6Hz, H-10β), 3.05 (1H, dd, $J_{9,10\alpha}$ = 5.4Hz and $J_{9,14}$ = 2.9Hz, H-9), 3.89 (3H, s, O-$\underline{C}H_3$), 4.84 (1H, s, H-5), 5.60 (1H, d, J = 8.8Hz, C^6=C$\underline{H}$-cyclohexyl), 6.56 (1H, d, $J_{1,2}$ = 8.2Hz, H-1), 6.68 (1H, d, $J_{2,1}$ = 8.2Hz, H-2).

δ_C (400MHz): 20.21 (C-10), 24.89 (C-8), 25.66, 25.77, 25.93 and 26.2 (C-7 and 3x$\underline{C}H_2$-cyclohexyl), 33.16 and 33.34 (2x$\underline{C}H_2$-cyclohexyl), 35.86 (C-15), 36.03 ($\underline{C}$H-cyclohexyl), 42.81 (C-14), 42.94 (N-$\underline{C}H_3$), 44.18 (C-13), 47.51 (C-16), 57.21 (O-$\underline{C}H_3$), 59.88 (C-9), 91.48 (C-5), 114.37 (C-2), 118.65 (C-1), 127.34 (C-11), 130.05 (C-12), 132.11 (C^6=$\underline{C}$H-cyclohexyl), 133.10 (C-6), 142.94 (C-3), 145.61 (C-4).

Catalytic hydrogenation of 138

a) at atmospheric pressure

138 (55mg, 0.15mmol) dissolved in absolute ethanol (10ml) was hydrogenated at atmospheric pressure and room temperature using palladium catalyst on charcoal

(8mg). TLC analysis of the reaction mixture after 5 days showed that no reaction had occurred.

b) at 45 atmospheres of pressure

The above reaction mixture was subjected to hydrogenation at 45 atmospheres of pressure and room temperature. TLC analysis of the reaction mixture after 24 hr revealed no reaction. The temperature of the reaction vessel was raised to 50°C for 21 hr. TLC analysis of the mixture again showed no reaction. Filtration of the reaction mixture over Celite and subsequent evaporation of ethanol under reduced pressure afforded starting material quantitatively.

c) using N,N-dimethylformamide as reaction solvent

Hydrogenation of **138** (133mg, 0.35mmol) in *N,N*-dimethylformamide (7ml) using palladium catalyst on charcoal (31mg) was performed at room temperature and 40 atmospheres of pressure. The disappearance of starting material was monitored by TLC and on complete reaction the reaction mixture was filtered over Celite and washed thoroughly with excess DMF. The filtrate was concentrated and the residue dissolved in EtOAc and washed with water (x3). After drying ($MgSO_4$), the organic solvent was removed under reduced pressure. Purification by column chromatography on silica gel using $CHCl_3$:MeOH:NH_3 (97:3:1) as eluent afforded **145** (87mg, 65%) and **146** (16mg, 8%) as colourless oils.

d) acid catalysed

To a mixture of **138** (540mg, 1.42mmol), palladium on charcoal (80mg) in absolute ethanol (20ml) was added conc. HCl (1 drop). The reaction mixture was hydrogenated at room temperature and atmospheric pressure. After 3 hr the mixture was filtered through Celite and then washed through with excess ethanol (2x20ml). The solvent was removed under reduced pressure and the resultant residue purified by

column chromatography using $CHCl_3$:MeOH:NH_3 (97:3:1) as eluent to give starting material **138** (430mg, 80%) and **145** (77mg, 14%) .

6-Cyclohexylmethyl-5,6-didehydro-4-hydroxy-3-methoxy-N-methylmorphinan (145)

R_f = 0.37 ($CHCl_3$:MeOH:NH_3 = 95:5:1); *m/z* (FAB) = 382.1(M^++H, 100%) ; IR (neat) = 3526 (OH), 1724 (C=C), 1606, 1581 (ArC-C), 1483 (C-N), 1278 (ArC-O-CH_3) cm^{-1}.

δ_H (400MHz) : 0.76-0.90 (2H, m, cyclohexyl-axial), 1.11-1.19 (3H, m, cyclohexyl-axial), 1.37-1.45 (1H, m, C<u>H</u>-cyclohexyl), 1.48-1.54 (2H, m, H-8_{ax} and H-8_{eq}), 1.62-1.72 (6H, m, H-15 and cyclohexyl-equitorial), 1.79-1.90 (5H, m, H-7, H-14, H-15, H-19_{ax} and H-19_{eq}), 2.02-2.22 (2H, m, H-7 and H-16_{ax}), 2.39 (3H, s, N-C<u>H</u>$_3$), 2.52 (1H, m, J_{gem} = 10.7Hz and $J_{16eq,15}$ = 2.9Hz, H-16_{eq}), 2.65 (1H, dd, J_{gem} = 18.1Hz and $J_{10\alpha,9}$ = 5.6Hz, H-10α), 2.92 (1H, br. s, H-9), 2.95 (1H, d, J_{gem} = 18.1Hz, H-10β), 3.82 (3H, s, O-C<u>H</u>$_3$), 5.95 (1H, br. s, OH), 6.23 (1H, s, H-5), 6.57 (1H, d, $J_{1,2}$ = 8.3Hz, H-1), 6.64 (1H, d, $J_{2,1}$ = 8.3Hz, H-2).

δ_C (400MHz) : 23.82 (C-10), 24.35 (C-8), 26.03, 26.34 and 26.73 (cyclohexyl-C<u>H</u>$_2$), 28.90 (C-7), 32.78 and 33.68 (cyclohexyl-C<u>H</u>$_2$), 35.69 (cyclohexyl-C<u>H</u>), 37.37 (C-15), 42.53 (N-C<u>H</u>$_3$), 43.95 (C-14), 45.95 (^{6}C-C<u>H</u>$_2$-cyclohexyl), 48.05 (C-16), 55.95 (O-C<u>H</u>$_3$), 57.93 (C-9), 108.05 (C-2), 118.15 (C-1), 127.84 (C-6), 129.74 (C-11), 130.93 (C-5), 134.08 (C-12), 144.17 (C-3), 144.76 (C-4).

HRMS (FAB) : found 382.2733, $C_{25}H_{36}NO_2$ (M^++H) requires 382.2746.

6-(Cyclohexylmethylidenyl)-4-hydroxy-3-methoxy-N-methylmorphinan (146)

R_f = 0.22 ($CHCl_3$:MeOH:NH_3 = 97:3:1); Mp. = 217-218°C; *m/z* (FAB) 382.3 (M^++H, 100%); IR (neat) = 3519 (OH), 1721, 1646, 1608, 1584, 1480, 1442, 1377, 1279, 1218, 1146, 1099, 1060 cm^{-1}.

δ_H (270MHz) : 0.66-0.82 (1H, m, $\underline{C}H_2$), 0.88-1.29 (6H, m, H-8, 5x$\underline{C}H_2$), 1.46-1.72 (6H, m, H-8, H-15_{ax}, 4x$\underline{C}H_2$), 1.74-1.92 (4H, m, H-5, H-7, H-14, H-15_{eq}), 1.94-2.06 (1H, m, $\underline{C}$H-cyclohexyl), 2.05 (1H, m, J_{gem} = 12.3Hz and $J_{16ax,15}$ = 3.5Hz, H-16_{ax}), 2.37 (3H, s, N-$\underline{C}H_3$), 2.42-2.54 (2H, m, H-16_{eq}, H-7), 2.60 (1H, dd, J_{gem} = 18.3Hz and $J_{10\alpha,9}$ = 5.5Hz, H-10α), 2.82 (1H, dd, $J_{9,10\alpha}$ = 5.6Hz and $J_{9,14}$ = 3.0Hz, H-9), 2.91 (1H, d, J_{gem} = 18.3Hz, H-10β), 3.83 (1H, dd, J_{gem} = 19.5Hz and $J_{5,19}$ = 1.5Hz, H-5), 3.84 (3H, s, O-$\underline{C}H_3$), 5.09 (1H, d, J_{gem} = 9.0Hz, H-19), 5.94 (1H, s, OH), 6.55 (1H, d, $J_{1,2}$ = 8.2Hz, H-1), 6.66 (1H, d, $J_{2,1}$ = 8.1Hz, H-2).

δ_C (400MHz) : 24.05 (C-10), 25.90 (C-8), 25.99, 26.15 and 28.44 (cyclohexyl-$\underline{C}H_2$), 28.82 (C-7), 33.41 and 33.80 (cyclohexyl-$\underline{C}H_2$), 35.95 (cyclohexyl-$\underline{C}$H), 37.95 (C-15), 40.11 (C-13), 42.78 (N-$\underline{C}H_3$), 45.50 (C-5), 47.00 (C-14), 47.66 (C-16), 56.49 (O-$\underline{C}H_3$), 57.68 (C-9), 108.39 (C-2), 118.01 (C-1), 125.47 (C-11), 128.97 (C-19), 131.71 (C-12), 134.18 (C-6), 144.51 (C-3), 144.64 (C-4).

HRMS (FAB) : found 382.2749, $C_{25}H_{36}NO_2$ (M^++H) requires 382.2746.

Reduction of 138 with triethylsilane and trifluroacetic acid[84]

To a stirred solution of **138** (699mg, 1.84mmol) in trifluroacetic acid (4ml) was added triethylsilane (0.3ml, 1.88mmol). After stirring at room temperature for 48 hr, the reaction mixture was adjusted to pH 9 by the addition of saturated $NaHCO_3$ and extracted with DCM (x3). The combined organic extracts were dried ($MgSO_4$) and solvent removed under reduced pressure. Purification of the resultant residue on silica gel using $CHCl_3$:MeOH:NH_3 (95:5:1) as eluent afforded a mixture of **145** (160mg, 23%) and **147** (340mg, 48%) as colourless oils.

6-Cyclohexylmethyl-4-hydroxy-3-methoxy-N-methylmorphinan (147)

R_f = 0.29 ($CHCl_3$:MeOH:NH_3 = 95:5:1); *m/z* (FAB) = 384.2 (M^++H, 100%); IR (Nujol) = 3522 (O-H), 1603 (ArC-C), 1582, 1481 (C-N), 1280 (ArC-O-CH_3) cm^{-1}.

δ_H (400MHz) : 0.71-0.90 (3H, m, H-5 and C$\underline{H}_2$), 0.93-1.55 (10H, m, H-6, H-8_{ax}, H-8_{eq}, C$\underline{H}$, H-19_{ax}, H-19_{eq} and 4xC$\underline{H}_2$), 1.59-1.74 (9H, m, H-7_{ax}, H-7_{eq}, H-14, H-15_{ax}, H-15_{eq}, 4xC$\underline{H}_2$), 2.08 (1H, m, J_{gem} = 12.2Hz and $J_{16ax,15}$ = 3.4Hz, H-16_{ax}), 2.40 (3H, s, N-C$\underline{H}_3$), 2.47 (1H, dd, J_{gem} = 12.2Hz and $J_{16eq,15}$ = 2.9Hz, H-16_{eq}), 2.67 (1H, dd, J_{gem} = 18.1Hz and $J_{10\alpha,9}$ = 5.9Hz, H-10α), 2.81 (1H, br. s, $J_{9,10\alpha}$ = 5.9Hz, H-9), 2.93 (1H, d, J_{gem} = 18.1Hz, H-10β), 3.36 (1H, d, J_{gem} = 12.7Hz, H-5), 3.84 (3H, s, O-C$\underline{H}_3$), 5.95 (1H, br. s, OH), 6.60 (1H, d, $J_{1,2}$ = 8.3Hz, H-1), 6.68 (1H, d, $J_{2,1}$ = 8.3Hz, H-2).

δ_C (400MHz) : 24.16 (C-10), 26.50 (C-8), 26.50, 26.85 and 27.29 (C$\underline{H}_2$), 30.71 (C$\underline{H}$), 33.80 (C$\underline{H}_2$), 33.96 (C-7), 34.03 (C$\underline{H}_2$), 34.42 (C-6), 37.93 (C-13), 38.22 (C-15), 42.67 (N-C$\underline{H}_3$), 43.95 (C-5), 45.59 (C^6-C$\underline{H}_2$-C_6H_{11}), 46.73 (C-14), 47.59 (C-16), 56.29 (O-C$\underline{H}_3$), 57.88 (C-9), 108.30 (C-2), 118.27 (C-1), 121.91 (C-11), 126.11 (C-12), 131.86 (C-3), 144.49 (C-4).

HRMS (FAB) : found 384.2906, $C_{25}H_{38}NO_2$ (M^++H) requires 384.2903.

Diimide[86] reduction of codeine (2)

To a warmed (60°C), stirred mixture of **2** (60mg, 0.20mmol), hydrazine hydrate (0.12ml, 3.97mmol) and 95% ethanol (1.5ml) was added hydrogen peroxide [27.5%] (0.25ml, 2.02mmol) dropwise. The temperature was maintained at 40°C and the reaction monitored by TLC. After the complete disappearance of starting material, the solution was cooled, diluted with water and then extracted with DCM (x3). The combined organic extracts were washed with sat. $NaHCO_3$, dried ($MgSO_4$) and evaporated to dryness. Column chromatography on silica gel eluting with $CHCl_3$:MeOH (9:1) afforded **118**α as a colourless oil (22mg, 37%).

Diimide reduction of 138

To a warmed (40°C), stirred mixture of **138** (475mg, 1.25mmol), hydrazine hydrate (1.17ml, 36mmol) and 95% ethanol (6ml) was added hydrogen peroxide [27.5%] (2.32ml, 19mmol) dropwise. The temperature was maintained at 40°C and the reaction stirred for 60 hr. The solution was cooled, diluted with sat. NaCl and then extracted with EtOAc (x3). The combined organic extracts were washed with sat. NaCl, $FeSO_4$ solution, sat. $NaHCO_3$, and saturated NaCl before being dried ($MgSO_4$) and evaporated to dryness. Purification by column chromatography on silica gel eluting with $CHCl_3$:MeOH (9:1) afforded **126β** as a pale yellow oil. Yield 233mg (49%).

6β-(Cyclohexylmethyl)dihydrodeoxycodeine (126β)

R_f = 0.51 ($CHCl_3$:MeOH = 9:1); *m/z* (FAB) = 382.2 (M^++H, 100%); IR (neat) = 1634, 1607 (ArC-C), 1501 (C-N), 1276 (ArC-O-CH_3) cm^{-1}.

δ_H (400MHz) : 0.72-0.96 (4H, m, H-7, H-8 and 2xCH_2-cyclohexyl), 1.09-1.25 (4H, m, 1xCH_2bridge and 3xCH_2-cyclohexyl), 1.28-1.46 (2H, m, H-6 and C<u>H</u>-cyclohexyl), 1.47-1.69 (9H, m, H-7, H-8, H-15_{eq}, 1xCH_2bridge and 5xCH_2-cyclohexyl), 1.76 (1H, m, J_{gem} = 12.9Hz and $J_{15,16}$ = 4.9Hz, H-15_{ax}), 2.10-2.16 (1H, m, H-14), 2.16 (1H, m, J_{gem} = 12.2Hz and $J_{16,15}$ = 3.9Hz, H-16_{ax}), 2.35 (1H, dd, J_{gem} = 18.6Hz and $J_{10\alpha,9}$ = 5.4Hz, H-10α), 2.39 (3H, s, N-C<u>H</u>$_3$), 2.50 (1H, dd, J = 12.2Hz and $J_{16eq,15}$ = 4.9Hz, H-16_{eq}), 3.00 (1H, d, J_{gem} = 18.6Hz, H-10β), 3.05 (1H, dd, $J_{9,10\alpha}$ = 4.9Hz and $J_{9,14}$ = 2.9Hz, H-9), 3.88 (3H, s, O-C<u>H</u>$_3$), 4.11 (1H, d, $J_{5,6}$ = 8.3Hz, H-5), 6.59 (1H, d, $J_{1,2}$ = 8.1Hz, H-1), 6.64 (1H, d, $J_{2,1}$ = 8.1Hz, H-2).

δ_C (400MHz) : 19.80 (C-10), 24.79 (C-8), 25.92, 26.01 and 26.34 (<u>C</u>H$_2$-cyclohexyl), 27.93 (C-7), 32.93 and 33.77 (<u>C</u>H$_2$-cyclohexyl), 34.28 (<u>C</u>H-cyclohexyl), 35.38 (C-15), 36.62 (C-6), 42.31 (C-13), 42.56 (N-<u>C</u>H$_3$), 43.09 (^{6}C-<u>C</u>H$_2$-cyclohexyl), 43.19

(C-14), 47.16 (C-16), 56.70 (O-$\underline{C}H_3$), 59.37 (C-9), 96.06 (C-5), 113.94 (C-2), 118.04 (C-1), 126.82 (C-11), 130.69 (C-12), 143.13 (C-3), 144.23 (C-4).

HRMS (FAB) : found 382.2750, $C_{25}H_{36}NO_2$ (M^++H) requires 382.2746.

Preparation of 2-(methyltriphenylphosphonium bromide)tetrahydro-2H-pyran (150)

A mixture of (±)-2-(bromomethyl)-tetrahydro-2H-pyran **149** (7.16ml, 56mmol), triphenylphosphine (14.66g, 56mmol) and toluene (25ml) were heated at reflux for 29 hr. After cooling the resultant solid was collected and then washed with toluene to afford the title compound as a white powder (17g, 69%).

Mp. = 233-235°C; *m/z* (FAB) = 361.1 (M-Br, 100%); IR (Nujol) = 1586, 1485, 1440, 1399, 1350, 1195, 1115, 1087, 1050, 1037, 994, 915, 850, 796, 763, 747, 714, 693 cm^{-1}.

δ_H (270MHz) : 1.35-1.61 (4H, m), 1.80 (1H, br. d, J = 5.3Hz), 2.23 (1H, br. d, J = 12.8Hz), 2.85 (1H, m, J = 11.4Hz and J = 1.0Hz), 3.46-3.65 (3H, m), 4.45 (1H, t, J = 13.4Hz), 7.63-7.85 (15H, m, ArC$\underline{H}$).

δ_C (400MHz) : 22.67 ($\underline{C}H_2$), 24.84 ($\underline{C}H_2$), 30.55 (CH-$\underline{C}H_2$-P^+), 32.29 ($\underline{C}H_2$-CH-$\underline{C}H_2$-P^+), 67.97 (-CH-$\underline{C}H_2$-O), 72.51 (CH), 119.23 (CH_2-P^+-Ar$\underline{C}$), 129.76, 129.89, 130.13, 133.77, 133.86, 134.02, 134.13, 134.41 (Ar$\underline{C}$H).

Found: C, 65.3; H, 5.9%. $C_{24}H_{26}BrOP$ requires: C, 65.3; H, 5.9%.

Wittig reaction between dihydrocodeinone (117) and 150

To a cooled, stirred suspension of **150** (3.32g, 7.52mmol) in THF (60ml) was added potassium *tert*-butoxide (0.71g, 6.33mmol) in one portion. After 1 hr, **117** (1.50g, 5.01mmol) was added to the deep red ylide solution. The mixture was stirred for a

further 15 min at 20°C, heated at reflux for 8 hr and then stirred overnight at room temperature. After removal of THF *in vacuo*, the resultant purple residue was purified by column chromatography on silica gel using $CHCl_3$:MeOH:NH_3 (97:3:1) as eluent to afford an unseparable 1:1 mixture of **153** and **154**. Overall yield 1.86g (97%).

6-(6-Hydroxyhex-2-enylidenyl)dihydrodeoxycodeine (153)

R_f = 0.28 ($CHCl_3$:MeOH:NH_3 = 97:3:1); *m/z* (FAB) = 382.1 (M^++H, 100%); IR (Nujol) : 3172 (OH), 1634 (ArC-C), 1602 (C=C-C=C), 1495 (C-N), 1257 (ArC-O-CH_3) 1070, 1037 (CH_2OH) cm^{-1}.

Found: C, 75.4; H, 8.2; N, 3.6. $C_{24}H_{31}NO_3$ requires: C, 75.6; H, 8.2; N, 3.7%.

6-(6-Hydroxyhex-2-enyl)deoxycodeine (154)

R_f = 0.22 ($CHCl_3$:MeOH:NH_3 = 97:3:1); *m/z* (FAB) = 382.2 (M^++H, 100%) ; IR (neat) = 3384 (OH), 1735, 1634, 1607 (ArC-C), 1503 (C-N), 1445, 1372 (ArC-O-CH_3) cm^{-1}.

δ_H (400MHz) : 0.84-0.94 (1H, m, H-8), 1.55-1.66 (3H, m, H-8, H-23_{ax}, H-23_{eq}), 1.70-1.81 (2H, m, H-15_{eq}, H-22), 1.89 (1H, m, J_{gem} = 12.2Hz and $J_{15ax,16}$ = 4.9Hz, H-15_{ax}), 2.12-2.15 (2H, m, H-7_{ax}, H-7_{eq}), 2.18 (1H, m, J_{gem} = 12.2Hz and $J_{16,15}$ = 3.9Hz, H-16_{ax}), 2.30 (1H, dd, J_{gem} = 18.6Hz and $J_{10\alpha,9}$ = 4.9Hz, H-10α), 2.27-2.33 (1H, m, H-14), 2.38 (3H, s, N-C<u>H</u>$_3$), 2.52 (1H, dd, J_{gem} = 12.2Hz and $J_{16eq,15}$ = 4.4Hz, H-16_{eq}), 2.66 (1H, m, J_{gem} = 11.2Hz, H-22), 2.82 (1H, br. s, O-<u>H</u>), 2.98 (1H, d, J_{gem} = 18.6Hz, H-10β), 3.05 (1H, dd, $J_{9,10\beta}$ = 4.9Hz and $J_{9,14}$ = 2.4Hz, H-9), 3.60 (2H, t, J = 6.6Hz, C<u>H</u>$_2$-OH), 3.88 (3H, s, O-C<u>H</u>$_3$), 4.90 (1H, s, H-5), 5.70 (1H, m, $J_{21,20}$ = 14.7Hz, $J_{21,22}$ = 7.3Hz, H-21), 6.20 (1H, dd, $J_{20,21}$ = 14.7Hz, $J_{20,19}$ = 11.2Hz, H-20), 6.37 (1H, d, $J_{19,20}$ = 10.7Hz, H-19), 6.58 (1H, d, $J_{1,2}$ = 8.3Hz, H-1), 6.68 (1H, d, $J_{2,1}$ = 8.3Hz, H-2).

δ_C (400MHz) : 19.96 (C-10), 25.25 (C-8), 25.39 (C-22), 29.07 (C-7), 32.14 (C-23), 35.41 (C-15), 42.71 (N-$\underline{C}H_3$), 42.75 (C-14), 44.05 (C-13) , 47.36 (C-16), 56.66 (O-$\underline{C}H_3$), 59.52 (C-9), 61.91 ($\underline{C}H_2$-OH), 90.48 (C-5), 113.74 (C-2), 118.62 (C-1), 124.73 (C-19), 125.61 (C-20), 126.84 (C-11), 129.45 (C-12), 134.41 (C-21), 135.63 (C-6), 142.76 (C-3), 144.98 (C-4).

HRMS (FAB) : found 382.2367, $C_{24}H_{32}NO_3$ (M^++H) requires 382.2382

Diimide reduction of alkenes 153 and 154

To a warmed (40°C), stirred unseparated mixture of alkenes **153** and **154** (541mg, 1.42mmol), hydrazine hydrate (0.88ml, 28mmol) and 95% ethanol (7ml) was added hydrogen peroxide [27.5%] (1.76ml, 14mmol) dropwise. The reaction mixture was maintained at 40°C for a further 8 hr and then stirred at room temperature overnight. The solution was diluted with sat. NaCl and extracted with EtOAc (x3). The combined organic extracts were washed with sat. NaCl, $FeSO_4$ solution, sat. $NaHCO_3$, and sat. NaCl before being dried ($MgSO_4$) and evaporated to dryness. Purification by column chromatography on silica gel eluting with $CHCl_3$:MeOH (9:1) afforded **159** as a white crystalline solid (115mg, 21%) and **160** (36mg, 7%) as a colourless oil.

6-(6-Hydroxyhexyl)dihydrodeoxycodeine (159)

R_f = 0.33 ($CHCl_3$:MeOH = 9:1); Mp. = 118-119°C; *m/z* (FAB) = 386.1 (M^++H, 100%) ; IR (neat) = 3378 (OH), 1633, 1606 (ArC-C), 1503 (C-N), 1276 (ArC-O-CH_3) cm^{-1}.

δ_H (400MHz) : 0.85-0.98 (2H, m, CH_2), 1.24-1.45 (8H, m), 1.49-1.66 (5H, m), 1.69 (1H, dd, J_{gem} = 12.2Hz and $J_{15eq,16eq}$ = 3.9Hz, H-15_{eq}), 1.85 (1H, m, J_{gem} = 12.2Hz and $J_{15ax,16eq}$ = 4.9Hz, H-15_{ax}), 2.22 (1H, m, J_{gem} = 12.2Hz and $J_{16ax,15eq}$ = 3.4Hz, H-16_{ax}), 2.20-2.30 (1H, m, H-14), 2.43 (1H, dd, J_{gem} = 18.1Hz

and $J_{10\alpha,9}$ = 5.4Hz, H-10α), 2.45 (3H, s, N-C$\underline{H}_3$), 2.59 (1H, dd, J_{gem} = 12.2Hz and $J_{16eq,15ax}$ = 4.4Hz, H-16$_{eq}$), 3.00 (1H, d, J_{gem} = 18.1Hz, H-10β), 3.13 (1H, br. s, H-9), 3.62 (2H, t, J_{gem} = 6.4 Hz, C$\underline{H}_2$-OH), 3.87 (3H, s, O-C$\underline{H}_3$), 4.16 (1H, d, J_{gem} = 7.8 Hz, H-5), 6.62 (1H, d, $J_{1,2}$ = 8.3Hz, H-1), 6.72 (1H, d, $J_{2,1}$ = 8.3Hz, H-2).

δ_C (400MHz) : 20.31 (C-10), 25.08 (C-8), 25.64, 26.65 and 27.63 (3x$\underline{C}H_2$), 29.50 (C-7), 32.77 and 34.60 (2x$\underline{C}H_2$), 35.35 (C-15), 40.01 (C-6), 42.45 (C-13), 42.67 (N-$\underline{C}H_3$), 42.98 (C-14), 47.68 (C-16), 56.77 (O-$\underline{C}H_3$), 59.95 (C-9), 62.98 ($\underline{C}H_2$-OH), 95.45 (C-5), 113.88 (C-2), 118.49 (C-1), 126.44 (C-11), 130.56 (C-12), 143.56 (C-3), 144.49 (C-4).

Found: C, 74.9; H, 9.2; N, 3.55%. $C_{24}H_{35}NO_3$ requires: C, 74.8; H, 9.15; N, 3.6%.

6-(6-Hydroxyhex-1-enylidene)dihydrodeoxycodeine (160)

R_f = 0.28 ($CHCl_3$:MeOH = 9:1); *m/z* (FAB) = 384.1 (M^++H, 100%) ; IR (neat) = 3378 (OH), 1715 (C=C), 1635, 1609 (ArC-C), 1501 (C-N), 1276 (ArC-O-CH_3) cm^{-1}.

δ_H (400MHz) : 0.79-0.94 (1H, m, CH_2), 1.11-1.17 (2H, m, H-8$_{ax}$ and H-8$_{eq}$), 1.24-1.32 (2H, m, CH_2), 1.44 (2H, m, C^6=CH-C$\underline{H}_2$), 1.51-1.81 (3H, m, H-7, H-15$_{eq}$ and CH_2), 1.90 (1H, m, J_{gem} = 12.7Hz and $J_{15ax,16}$ = 4.9Hz, H-15$_{ax}$), 1.91-2.00 (2H, m, CH_2), 2.04 (1H, s, OH), 2.20 (1H, m, J_{gem} = 12.2Hz and $J_{16,15eq}$ = 3.9Hz, H-16$_{ax}$), 2.28-2.30 (1H, m, H-14), 2.32 (1H, dd, J_{gem} = 18.1Hz and $J_{10\alpha,9}$ = 5.4Hz, H-10α), 2.40 (3H, s, N-C$\underline{H}_3$), 2.45 (1H, m, J_{gem} = 14.2Hz and $J_{7,8}$ = 3.4Hz, H-7), 2.54 (1H, dd, J_{gem} = 12.2Hz and $J_{16eq,15ax}$ = 4.4Hz, H-16$_{eq}$), 2.98 (1H, d, J_{gem} = 18.6Hz, H-10β), 3.07 (1H, dd, $J_{9,10\alpha}$ = 5.4Hz, H-9), 3.53 (1H, t, J = 6.4, Hz, C^6=CH-C$\underline{H}_2$), 3.62 (1H, t, J = 6.4Hz, C^6=CH-C$\underline{H}_2$), 3.89 (3H, s, O-C$\underline{H}_3$), 4.87 (1H, s, H-5), 5.74 (1H, t, J = 7.3Hz, C^6=C$\underline{H}$), 6.59 (1H, d, $J_{1,2}$ = 8.3Hz, H-1), 6.69 (1H, d, $J_{2,1}$ = 8.3Hz, H-2).

δ_C (400MHz) : 20.14 (C-10), 24.82 (C-7), 24.91 (C-8), 25.55, 26.74 and 29.19 ($\underline{C}H_2$), 32.61 (C^6=CH-$\underline{C}H_2$), 35.57 (C-15), 42.49 (N-$\underline{C}H_3$), 42.85 (C-14), 44.18 (C-13), 47.53 (C-16), 56.86 (O-$\underline{C}H_3$), 59.73 (C-9), 62.82 ($\underline{C}H_2$-OH), 91.15 (C-5), 113.77 (C-2), 118.65 (C-1), 125.62 (C^6=$\underline{C}$H-CH_2), 127.08 (C-11), 129.88 (C-12), 134.47 (C-6), 142.92 (C-3), 145.34 (C-4).

HRMS (FAB) : found 384.2543, $C_{24}H_{34}NO_3$ (M^++H) requires 384.2539.

Catalytic reduction of 153 using palladium on charcoal

153 (219mg, 0.57mmol) in 95% ethanol (20ml) was hydrogenated at room temperature at atmospheric pressure using palladium on charcoal (36mg) as catalyst. The disappearance of starting material was monitored by TLC and on completion the mixture was filtered through Celite and the filter contents washed thoroughly with excess ethanol. The filtrate was concentrated under diminished pressure to afford a colourless oil. Purification by column chromatography on silica gel using $CHCl_3$:MeOH (97:3) as eluent afforded 5,6-dihydro-4-hydroxy-6-(6-hydroxyhexyl)-3-methoxy-*N*-methylmorphinan (61mg, 28%) as a colourless oil.

5,6-Dihydro-4-hydroxy-6-(6-hydroxyhexyl)-3-methoxy-N-methylmorphinan

R_f = 0.28 ($CHCl_3$:MeOH = 9:1); *m/z* (FAB) = 386.3 (M^++H, 100%); IR (neat) = 3516, 3312 (OH), 1723, 1661, 1607 (ArC-C), 1580, 1480 (C-N), 1442, 1278 (ArC-Ȯ-CH_3), 1146, 1108, 1057, 936, 849, 793, 743 cm^{-1}.

δ_H (400MHz) : 1.28-1.37 (4H, m, CH_2), 1.44 (2H, m, CH_2), 1.50-1.59 (4H, m, H-8_{ax} and H-8_{eq}, H-15_{ax} and H-15_{eq}), 1.68 (1H, m, J = 12.2Hz and J = 4.9Hz, CH_2), 1.85-1.92 (3H, m, CH_2, H-14), 1.97-2.12 (3H, m, CH_2, H-7_{ax} and H-7_{eq}), 2.09 (1H, m, J_{gem} = 12.2Hz and $J_{16ax,15eq}$ = 3.4Hz, H-16_{ax}), 2.17, (1H, s, OH), 2.41 (3H, s, N-$\underline{C}H_3$), 2.54 (1H, dd, J_{gem} = 12.2Hz and $J_{16eq,15}$ = 2.9Hz, H-16_{eq}), 2.69 (1H, dd, J_{gem} = 18.1Hz and $J_{10\alpha,9}$ = 5.9Hz, H-10α), 2.94-2.97 (1H, m, H-9), 2.95 (1H, d,

J_{gem} = 18.1Hz, H-10β), 3.63 (1H, t, J = 6.8Hz, $C^6(CH)_5C\underline{H}_2OH$), 3.83 (3H, s, O-$C\underline{H}_3$), 5.95 (1H, br. s, OH), 6.28 (1H, s, H-5), 6.58 (1H, d, $J_{1,2}$ = 8.3Hz, H-1), 6.65 (1H, d, $J_{2,1}$ = 8.3Hz, H-2).

δ_C (400MHz) : 23.91 (C-10), 24.29 (C-8), 25.54, 27.49, 28.63 and 28.70 ($\underline{C}H_2$), 32.78 (C-15), 37.00 (C-19), 37.22 (C-13), 37.28 (C-7), 42.45 (N-$\underline{C}H_3$), 43.59 (C-14), 48.18 (C-16), 55.99 (O-$\underline{C}H_3$), 58.09 (C-9), 63.01 ($\underline{C}H_2$-OH), 108.16 (C-2), 118.26 (C-1), 124.18 (C-6), 127.75 (C-11), 129.41 (C-5), 135.49 (C-12), 144.19 (C-3), 144.87 (C-4).

HRMS (FAB) : found 386.2682, $C_{24}H_{36}NO_3$ (M^++H) requires 386.2695.

Preparation of 6-(n-hexylidenyl)dihydrodeoxycodeine (162)

To a cooled, stirred suspension of *n*-hexyltriphenylphosphonium bromide (1.72g, 4.02mmol) in THF (20ml) was added potassium *tert*-butoxide (0.45g, 4.01mmol) in one portion. After 1hr, **117** (1.00g, 3.34mmol) was added to the deep orange ylide solution. The mixture was stirred for 1 hr at 20°C before being heated at reflux for 5 hr. After cooling, THF was removed *in vacuo* and the residue dissolved in chloroform and then washed with water (x3). The organic phase was dried ($MgSO_4$) and chloroform removed under reduced pressure. Purification by column chromatography using $CHCl_3$:MeOH (94:6) as eluent afforded **162** as a colourless oil (775mg, 63%) in a 6.8:1 ratio of unseparable *E:Z* isomers.

(E)-162

R_f = 0.60 ($CHCl_3$:MeOH = 9:1); *m/z* (FAB) : 368.1 (M^++H, 100%); IR (neat) = 1634 (C=C), 1606 (ArC-C), 1501 (C-N), 1445, 1372, 1334, 1276 (ArC-O-CH_3), 1201, 1151, 1105, 1042, 909, 862 cm^{-1}.

δ_H (400MHz) : 0.89 (3H, t, J = 6.8Hz, C^6=CH$(CH_2)_4\underline{C}H_3$), 0.91-0.99 (1H, m, CH_2), 1.32-1.41 (6H, m, CH_2, H-8_{ax} and H-8_{eq}), 1.45-1.52 (1H, m, CH_2), 1.74 (1H, m, J_{gem} = 12.2Hz, $J_{15eq,16eq}$ = 3.4Hz, H-15_{eq}), 1.88 (1H, td, J_{gem} = 12.2Hz and $J_{15ax,16eq}$ = 4.9Hz, H-15_{ax}), 2.02-2.08 (2H, m, CH_2), 2.16 (1H, m, $J_{14,8ax}$ = 12.2Hz, $J_{14,8eq}$ = 5.4Hz and $J_{14,9}$ = 2.9Hz, H-14), 2.20-2.35 (2H, overlap, CH_2), 2.25 (1H, m, J = 12.2Hz and J =3.9Hz, CH_2), 2.33 (1H, dd, J_{gem} = 18.6Hz and $J_{10,9}$ = 5.9Hz, H-10α), 2.40 (3H, s, N-$\underline{C}H_3$), 2.50 (1H, dd, J_{gem} = 12.2Hz, $J_{16eq,15eq}$ = 3.4Hz, H-16_{eq}), 2.98 (1H, d, J_{gem} = 18.6Hz, H-10β), 3.07 (1H, dd, $J_{9,10\alpha}$ = 5.9Hz, $J_{9,14}$= 2.9Hz, H-9), 3.84 (3H, s, O-$\underline{C}H_3$), 5.19 (1H, s, H-5), 5.31 (1H, t, J = 7.3Hz, C^6=$\underline{C}H(CH_2)_4CH_3$), 6.58 (1H, d, $J_{1,2}$ = 7.8Hz, H-1), 6.69 (1H, d, $J_{2,1}$ = 7.8Hz, H-2).

δ_C (400MHz) : 14.03 (C^6=CH$(CH_2)_4\underline{C}H_3$), 19.92 (C-10), 22.58 (C-8), 24.44, 28.63, 29.69, 31.45, 31.63 (5xCH_2), 36.40 (C-15), 41.41 (C-14), 42.93 (N-$\underline{C}H_3$), 43.62 (C-13), 46.99 (C-16), 56.34 (O-$\underline{C}H_3$), 59.79 (C-9), 89.36 (C-5), 113.23 (C-2), 118.28 (C-1), 127.20 (C-11), 129.83 (C-12), 132.16 (C^6=$\underline{C}H(CH_2)_4CH_3$), 133.58 (C-6), 142.34 (C-3), 145.42 (C-4).

HRMS (FAB) : found 368.2591, $C_{24}H_{34}NO_2$ (M^++H) requires 368.2590.

(Z)-162

δ_H (400MHz) : contains 4.87 (1H, s, H-5), 5.73 (1H, t, J = 7.3Hz, C^6=$\underline{C}H(CH_2)_4CH_3$).

δ_C (400MHz) : 13.94 (C^6=CH$(CH_2)_4\underline{C}H_3$), 20.02 (C-10), 22.39 (C-8), 24.72, 25.46, 26.73, 29.09, 31.01 (5xCH_2), 35.69 (C-15), 41.23 (C-14), 42.86 (N-$\underline{C}H_3$), 44.10 (C-13), 47.47 (C-16), 56.68 (O-$\underline{C}H_3$), 59.66 (C-9), 91.19 (C-5), 113.61 (C-2), 118.53 (C-1), 125.88 (C^6=$\underline{C}H(CH_2)_4CH_3$), 127.09 (C-11), 130.80 (C-12), 134.59 (C-6), 142.80 (C-3), 145.42 (C-4).

Diimide reduction of 162

To a cooled stirred mixture of **162** (585mg, 1.59mmol), hydrazine hydrate (0.99ml, 32mmol) in 95% ethanol (4.5ml) was added hydrogen peroxide [27.5%] (1.97ml, 16mmol) dropwise. The mixture was then stirred for 16 hr at 30-40°C before a further 0.99ml of hydrazine hydrate (32mmol) and 1.97ml of hydrogen peroxide (16mmol) was added. After 7 hr, the mixture was cooled to ambient temperature and all solvent removed under reduced pressure. The resultant residue was purified by column chromatography using $CHCl_3$:MeOH (95:5) as eluent affording **163** as a colourless oil (300mg, 51%).

6β-(n-Hexyl)dihydrodeoxycodeine (163)

R_f = 0.60 ($CHCl_3$:MeOH = 9:1); *m/z* (FAB) : 370.3 (M^++H, 100%); IR (neat) = 1632, 1607 (ArC-C), 1500(C-N), 1443, 1372, 1341, 1276 (ArC-O-CH_3), 1202, 1152, 1042, 926, 855, 795, 752 cm^{-1}.

δ_H (400MHz) : 0.87 (3H, t, J = 6.4Hz, C^6H-C_5H_{10}-$C\underline{H}_3$), 0.88-0.96 (2H, m, CH_2), 1.21-1.39 (10H, br. s, H-6 and CH_2), 1.46-1.54 (1H, m, CH_2), 1.66 (1H, br.d, J_{gem} = 12.2Hz, H-15_{eq}), 1.62-1.76 (2H, m, CH_2), 1.77 (1H, m, J_{gem} = 12.2Hz and J15ax,16eq = 4.9Hz, H-15_{ax}), 2.12-2.17 (1H, m, H-14), 2.16 (1H, m, J_{gem} = 12.2Hz, $J_{16ax,15}$ = 3.4Hz, H-16_{ax}), 2.35 (1H, dd, J_{gem} = 18.6Hz and $J_{10\alpha,9}$ = 5.4Hz, H-10α), 2.39 (3H, s, N-$C\underline{H}_3$), 2.50 (1H, dd, J_{gem} = 12.2Hz, $J_{16eq,15}$ = 3.9Hz, H-16_{eq}), 2.99 (1H, d, J_{gem} = 18.1Hz, H-10β), 3.05 (1H, br.s, H-9), 3.87 (3H, s, O-$C\underline{H}_3$), 4.15 (1H, d, $J_{5,6}$ = 7.8Hz, H-5), 6.59 (1H, d, $J_{1,2}$ = 7.8Hz, H-1), 6.69 (1H, d, $J_{2,1}$ = 8.3Hz, H-2).

δ_C (400MHz) : 13.94 (C^6H-C_5H_{10}-$\underline{C}H_3$), 19.98 (C-10), 22.47, 24.97,26.54, 27.57, 29.32, 31.65, 34.61 and 35.61, (8x$\underline{C}H_2$), 35.58 (C-15), 39.95 (C-6), 42.44 (C-13), 42.71 (N-$\underline{C}H_3$), 43.35 (C-14), 47.39 (C-16), 56.55 (O-$\underline{C}H_3$), 59.57 (C-9), 95.38 (C-5),

113.67 (C-2), 118.20 (C-1), 126.84 (C-11), 130.66 (C-12), 143.22 (C-3), 144.30 (C-4).

HRMS (FAB) : found 370.2724, $C_{24}H_{36}NO_2$ (M^++H) requires 370.2746.

Preparation of 6-(dimethylaminoethylidenyl)dihydrodeoxycodeine (165)

To a cooled, stirred suspension of dimethylaminoethyltriphenylphosphine bromide (4.15g, 10mmol) in THF (35ml) was added potassium *tert*-butoxide (1.12g, 10mmol) in one portion. After 1 hr, **117** (1.50g, 5.01mmol) was added to the pale yellow ylide solution. The mixture was stirred for 1 hr at 20°C before being heated at reflux for 6 hr. After cooling, THF was removed *in vacuo* and the residue dissolved in chloroform and then washed with water (x3). The organic phase was dried ($MgSO_4$) and chloroform removed under reduced pressure. Purification by column chromatography using $CHCl_3$:MeOH:NH_3 (90:10:1) as eluent afforded **165** as a colourless oil (1.04g, 58%) in a 8:1 ratio of unseparable *E:Z* isomers.

(E)-165

R_f = 0.26 ($CHCl_3$:MeOH:NH_3 = 90:10:1); *m/z* (FAB) : 355.3 (M^++H, 100%); IR (neat) = 1635 (C=C), 1606 (ArC-C), 1503(C-N), 1440, 1374, 1337, 1320, 1276 (ArC-O-CH_3), 1260, 1198, 1178, 1148, 1101, 1056, 1040, 1020, 911, 860, 790 cm^{-1}.

δ_H (400MHz) : 0.95 (1H, m, J_{gem} = 12.2Hz and $J_{8,7}$ = 4.9Hz, H-8_{ax}), 1.51 (1H, m, J_{gem} = 12.2Hz and $J_{8,7}$ = 3.9Hz, H-8_{eq}), 1.73 (1H, dd, J_{gem} = 12.2Hz, H-15_{eq}), 1.89 (1H, m, J_{gem} = 12.2Hz and J15ax,16eq = 4.9Hz, H-15_{ax}), 2.10-2.24 (3H, m, H-7_{ax}, H-7_{eq} and H-14), 2.23 (1H, m, J_{gem} = 12.2Hz, $J_{16ax,15}$ = 3.9Hz, H-16_{ax}), 2.25 (6H, s, C^6=CHCH_2N(CH_3)2), 2.34 (1H, dd, J_{gem} = 18.6Hz and $J_{10\alpha,9}$ = 5.4Hz, H-10α), 2.40 (3H, s, N-CH_3), 2.52 (1H, dd, J_{gem} = 12.2Hz, $J_{16eq,15}$ = 3.9Hz, H-16_{eq}), 2.99 (1H, d, J_{gem} = 18.6Hz, H-10β), 3.08 (1H, dd, $J_{9,10\alpha}$ = 5.4Hz and $J_{9,14}$ = 2.9Hz, H-9), 3.26 (2H, t, J = 6.8Hz, C^6=CHCH_2N(CH_3)2), 3.85 (3H, s, O-CH_3), 5.16

(1H, s, H-5), 5.38 (1H, t, J = 6.83Hz, C^6=C<u>H</u>$CH_2N(CH_3)_2$), 6.60 (1H, d, $J_{1,2}$ = 8.3Hz, H-1), 6.70 (1H, d, $J_{2,1}$ = 8.3Hz, H-2).

δ_C (400MHz) : 19.94 (C-10), 24.62 (C-8), 32.07 (C-7), 36.16 (C-15), 41.91 (C-14), 42.93 (N-<u>C</u>H_3), 43.86 (C-13), 45.38 (-N(<u>C</u>$H_3)_2$), 47.08 (C-16), 56.39 (O-<u>C</u>H_3), 57.43 (C^6=CH<u>C</u>$H_2N(CH_3)_2$), 59.74 (C-9), 89.25 (C-5), 113.36 (C-2), 118.59 (C-1), 127.16 (C-11), 129.05 (C^6=<u>C</u>$HCH_2N(CH_3)_2$), 129.69 (C-12), 136.20 (C-6), 142.49 (C-3), 145.00 (C-4).

HRMS (FAB) : found 355.2378, $C_{22}H_{31}N_2O_2$ (M^++H) requires 355.2386.

(Z)-165

δ_H (400MHz) contains 4.89 (1H, s, H-5), 5.88 (1H, t, J = 6.83Hz, C^6=C<u>H</u>$CH_2N(CH_3)_2$).

δ_C (400MHz) contains 90.73 (C-5), 122.24 (C^6=<u>C</u>$HCH_2N(CH_3)_2$).

Diimide reduction of 165

To a cooled stirred mixture of **165** (1.71g, 4.82mmol), hydrazine hydrate (3ml, 96mmol) in 95% ethanol (8ml) was added hydrogen peroxide [27.5%] (5.96ml, 48mmol) dropwise over 30 min. The mixture was then stirred for 3 hr at 30-40°C before a further 3ml of hydrazine hydrate (96mmol) and 5.96ml of hydrogen peroxide (48mmol) was added. The mixture was then stirred for a further 20 hr at 30-40°C. The mixture was then cooled, concentrated to half its original volume and then extracted with chloroform (x4). The organic phase was dried ($MgSO_4$), and the solvent removed under reduced pressure. The resultant residue was purified by column chromatography using as eluent $CHCl_3$:MeOH:NH_3 (90:10:2) and then $CHCl_3$:MeOH:NH_3 (95:5:2) to afford **166** (260mg, 15%) and **167** (141mg, 8%) as colourless oils.

6β-(Dimethylaminoethyl)dihydrodeoxycodeine (166)

R_f = 0.33 ($CHCl_3$:MeOH:NH_3 = 90:10:2); *m/z* (FAB) : 357.1 (M^++H, 100%); IR (neat) = 1634, 1608 (ArC-C), 1500(C-N), 1443, 1276 (ArC-O-CH_3), 1152, 1106, 1056, 1044, 924, 852 cm^{-1}.

δ_H (400MHz) : 0.92 (1H, t, J = 12.2Hz, H-7_{ax}), 0.92 (1H, t, J = 12.2Hz, H-8_{ax}), 1.27-1.36 (1H, m, H-6), 1.37-1.46 (1H, m, $C^6HC\underline{H_2}CH_2N(CH_3)_2$), 1.46-1.51 (1H, m, H-$8_{eq}$), 1.64-1.68 (2H, m, H-$7_{eq}$ and H-15_{eq}), 1.77 (1H, m, J_{gem} = 12.2Hz and $J_{15ax,16eq}$ = 4.9Hz, H-15_{ax}), 1.88-1.96 (1H, m, $C^6HC\underline{H_2}CH_2N(CH_3)_2$), 2.11-2.17 (1H, m, H-14), 2.16 (1H, m, J_{gem} = 12.2Hz, $J_{16ax,15}$ = 4.4Hz, H-16_{ax}), 2.20 (6H, s, $C^6HCH_2CH_2N(C\underline{H_3})_2$), 2.26 (1H, m, J_{gem} = 11.7Hz and J = 4.4Hz, $C^6HCH_2C\underline{H_2}N(CH_3)_2$), 2.34 (1H, dd, J_{gem} = 18.1Hz and $J_{10\alpha,9}$ = 5.4Hz, H-10α), 2.35-2.42 (1H, m, $C^6HCH_2C\underline{H_2}N(CH_3)_2$), 2.39 (3H, s, N-$C\underline{H_3}$), 2.49 (1H, dd, J_{gem} = 12.2Hz, $J_{16eq,15}$ = 3.9Hz, H-16_{eq}), 2.99 (1H, d, J_{gem} = 18.1Hz, H-10β), 3.04 (1H, dd, $J_{9,10\alpha}$ = 4.9Hz and $J_{9,14}$ = 2.9Hz, H-9), 3.87 (3H, s, O-$C\underline{H_3}$), 4.16 (1H, d, $J_{5,6}$= 8.3Hz, H-5), 6.59 (1H, d, $J_{1,2}$ = 8.3Hz, H-1), 6.69 (1H, d, $J_{2,1}$ = 8.3Hz, H-2).

δ_C (400MHz) : 20.02 (C-10), 24.93 (C-8), 27.66 (C-7), 32.73 ($C^6H\underline{C}H_2CH_2N(CH_3)_2$), 35.65 (C-15), 38.23 (C-6), 42.58 (C-13), 42.82 (N-$\underline{C}H_3$), 43.41 (C-14), 45.31 and 45.31 (-N($\underline{C}H_3)_2$), 47.47 (C-16), 56.74 (O-$\underline{C}H_3$), 57.07 ($C^6HCH_2\underline{C}H_2N(CH_3)_2$), 59.59 (C-9), 95.43 (C-5), 113.91 (C-2), 118.40 (C-1), 127.05 (C-11), 130.69 (C-12), 143.35 (C-3), 144.32 (C-4).

HRMS (FAB) : found 357.2535, $C_{22}H_{33}N_2O_2$ (M^++H) requires 357.2542.

6β-(Dimethylaminoethyl)dihydrodeoxycodeine-N-oxide (167)

R_f = 0.13 ($CHCl_3$:MeOH:NH_3 = 90:10:2); *m/z* (FAB) : 373.1 (M^++H, 100%); IR (neat) = 1634, 1610 (ArC-C), 1501 (C-N), 1444, 1373, 1326, 1276 (ArC-O-CH_3), 1214, 1152, 1067, 1048, 922, 852 cm^{-1}.

δ_H (400MHz) : 0.93 (1H, m, J_{gem} = 12.2Hz, $J_{8ax,7eq}$ = 2.3Hz, H-8_{ax}), 1.09 (1H, m, J_{gem} = 12.2Hz, J = 1.5Hz, H-7_{ax}), 1.28-1.38 (1H, m, H-6), 1.51-1.57 (1H, m, H-8_{eq}), 1.64-1.69 (2H, m, H-7_{eq} and H-15_{eq}), 1.79 (1H, m, J_{gem} = 12.2Hz and $J_{15ax,16eq}$ = 4.9Hz, H-15_{ax}), 2.07 (2H, m, $C^6HC\underline{H}_2CH_2N(CH_3)_2$), 2.12-2.22 (1H, m, H-14), 2.15 (1H, m, J_{gem} = 12.2Hz, $J_{16ax,15eq}$ = 4.4Hz, H-16_{ax}), 2.35 (1H, dd, J_{gem} = 18.6Hz and $J_{10\alpha,9}$ = 5.3Hz, H-10α), 2.39 (3H, s, N-$C\underline{H}_3$), 2.51 (1H, dd, J_{gem} = 12.2Hz, $J_{16eq,15eq}$ = 3.9Hz, H-16_{eq}), 3.01 (1H, d, J_{gem} = 18.6Hz, H-10β), 3.07 (1H, dd, H-9), 3.19 (3H, s, $C^6HCH_2CH_2N(C\underline{H}_3)_2$), 3.22 (3H, s, $C^6HCH_2CH_2N(C\underline{H}_3)_2$), 2.29-2.40 (1H, m, $C^6HCH_2C\underline{H}_2N(CH_3)_2$), 3.42-3.52 (1H, m, $C^6HCH_2C\underline{H}_2N(CH_3)_2$), 3.85 (3H, s, O-$C\underline{H}_3$), 4.23 (1H, d, $J_{5,6}$ = 8.3Hz, H-5), 6.64 (1H, d, $J_{1,2}$ = 8.3Hz, H-1), 6.71 (1H, d, $J_{2,1}$ = 8.3Hz, H-2).

δ_C (400MHz) : 20.03 (C-10), 24.89 (C-8), 28.53 (C-7), 29.41 ($C^6H\underline{C}H_2CH_2N(CH_3)_2$), 35.63 (C-15), 38.50 (C-6), 42.87 (N-$\underline{C}H_3$), 42.90 (C-13), 43.23 (C-14), 47.42 (C-16), 56.44 (O-$\underline{C}H_3$), 58.10 ($C^6HCH_2CH_2N(\underline{C}H_3)_2$), 59.35 ($C^6HCH_2CH_2N(\underline{C}H_3)_2$), 59.51 (C-9), 69.62 ($C^6HCH_2\underline{C}H_2N(CH_3)_2$), 95.02 (C-5), 113.29 (C-2), 118.96 (C-1), 127.05 (C-11), 130.30 (C-12), 143.42 (C-3), 143.79 (C-4).

HRMS (FAB) : found 373.2489, $C_{22}H_{33}N_2O_2$ (M^++H) requires 373.2489.

Attempted Wittig reaction between dihydrocodeinone and cyclohexyltriphenylphosphonium bromide

To a stirred suspension of cyclohexyltriphenylphosphonium bromide (2.16g, 5.08mmol) in THF (50ml), maintained at 20°C was added potassium *tert*-butoxide (0.56g, 4.99mmol) in one portion. After 1 hr, dihydrocodeinone (1.00g, 3.34mmol) was added to the deep red ylide solution. The mixture was stirred for a further 90 min at 20°C and then heated under reflux for 18 hr. THF was then removed *in vacuo* and the residue dissolved in DCM and washed three times with water. The organic phase

was dried ($MgSO_4$) and DCM removed under reduced pressure. Purification of the resultant residue by column chromatography using $CHCl_3$:MeOH:NH_3 (90:10:1) as eluent afforded 690mg (35%) of **173**.

Codeine 'dimer' (173)

R_f = 0.20 ($CHCl_3$:MeOH:NH_3 = 90:10:1); *m/z* (FAB) 599.2 (M^++H, 100%); IR (Nujol) 3333 (OH), 1709, 1631, 1604, 1498, 1376, 1278 cm^{-1}.

δ_H (270MHz) : 0.32-0.51 (1H, m), 0.85-1.14 (4H, m), 1.22-1.34 (1H, m), 1.57-1.67 (1H, m), 1.88-2.15 (5H, m), 2.27 (1H, m, J_{gem} = 12.1Hz and J = 3.5Hz, H-16$_{ax}$), 2.36 (3H, s, N-C$\underline{H}_3$), 2.37 (3H, s, N-C$\underline{H}_3$), 2.35-2.73 (6H, m), 2.83 (2H, br. s), 2.99 (1H, d, J_{gem} = 18.7Hz, H-10β), 3.18 (1H, m, $J_{9,14}$ = 3.5Hz, H-9), 3.81 (3H, s, O-C$\underline{H}_3$), 3.90 (3H, s, O-C$\underline{H}_3$), 5.01 (1H, s, H-5), 5.96 (1H, s, OH), 6.59 (1H, d, $J_{1,2}$ = 8.2Hz, H-1), 6.60 (1H, d, $J_{1,2}$ = 8.1Hz, H-1), 6.65 (1H, d, $J_{2,1}$ = 8.4Hz, H-2), 6.71 (1H, d, $J_{2,1}$ = 8.2Hz, H-2).

δ_C (400MHz) : 19.73 (C-10), 20.28, 21.51 (C-8, C-8), 24.29 (C-10), 27.25 (C-7), 30.16 (C-14), 31.20, 34.71 (C-15, C-15), 38.86 (C-14), 40.34 (C-13), 42.45, 43.07 (N-$\underline{C}H_3$, N-$\underline{C}H_3$), 43.29 (C-13), 46.45, 46.63 (C-16, C-16), 55.94, 57.13 (O-$\underline{C}H_3$, O-$\underline{C}H_3$), 57.62, 59.40 (C-9, C-9), 82.95 (C-6), 85.37 (C-5), 88.26 (C-5), 108.45 (C-2), 114.54 (C-2), 115.38 (C-7), 118.98, 119.04, (C-1, C-1), 125.46, 126.92 (C-11, C-11), 129.68, 131.18 (C-12, C-12), 142.70, 143.31 (C-3, C-3), 144.87 (C-6), 144.99, 149.40 (C-4, C-4).

HRMS (FAB) : found 599.3104, $C_{36}H_{43}N_2O_6$ (M^++H) requires 599.3121.

Dehydration of 173

To a solution of **173** (281mg, 0.47mmol) in DCM (3ml) was added 2M HCl (2ml) and the mixture stirred overnight at room temperature. The mixture was then adjusted to

pH 9 by the addition of aqueous K_2CO_3 and extracted three times with DCM. The organic layer was dried ($MgSO_4$) and DCM removed under reduced pressure to afford a brown oil. Purification by column chromatography using $CHCl_3$:CH_3OH:NH_3 (90:10:1) as eluent afforded 135mg (50%) of **174** as a pale brown solid.

Compound 174

R_f = 0.48 ($CHCl_3$:MeOH:NH_3 = 90:10:1); *m/z* (FAB) 581.2 (M^++H, 100%); IR (neat) 3507 (OH), 1722, 1676, 1632 (C=C), 1605 (ArC-C), 1579, 1503 (C-N) cm^{-1}

δ_H (270MHz) : 1.62-1.76 (2H, m, H-8_{ax}, H-8_{eq}), 1.82-2.01 (5H, m, H-8, H-14, 3xH-15), 2.38 (3H, s, N-C<u>H</u>3), 2.43 (3H, s, N-C<u>H</u>3), 2.12-2.58 (10H, m, 2xH-7, H-8, H-10α, H-14, H-15, 4xH-16), 2.71 (1H, dd, J_{gem} = 18.0Hz and J = 5.1Hz, H-10α), 2.93 (1H, dd, J = 3.5Hz, H-9), 3.01 (1H, d, J_{gem} = 18.3Hz, H-10β), 3.07 (1H, d, J_{gem} = 18.3Hz, H-10β), 3.20 (1H, dd, $J_{9,10\alpha}$ = 5.7Hz, $J_{9,14}$ = 2.8Hz, H-9), 3.82 (3H, s, O-C<u>H</u>3), 3.84 (3H, s, O-C<u>H</u>3), 5.53 (1H, s, H-5), 6.62 (1H, d, J = 8.4Hz, H-1), 6.66 (1H, d, J = 8.4Hz, H-1), 6.69 (1H, d, J = 8.4Hz, H-2), 6.73 (1H, d, J = 8.2Hz, H-2), 7.46 (1H, br. s, OH).

δ_C (400MHz) : 20.16 (C-7), 20.25 (C-10), 21.20 (C-8), 24.00 (C-10), 24.00 (C-8), 33.37, 35.65 (C-15, C-15), 37.22 (C-13), 41.39 (C-14), 42.44, 42.93 (N-<u>C</u>H3, N-<u>C</u>H3), 44.30 (C-14), 44.52 (C-13), 46.40, 46.81 (C-16, C-16), 55.73, 56.30 (O-<u>C</u>H3, O-<u>C</u>H3), 57.03, 59.44 (C-9, C-9), 84.50 (C-5), 109.52 (C-2), 113.39 (C-2), 118.42, 118.53, 118.73 (C-1, C-1, C-7), 123.01, 124.60 (C-11, C-11), 126.95, 128.48 (C-12, C-12), 128.68 (C-5), 143.06, 144.54, 144.74, 145.25, 146.46, (C-3, C-3, C-4, C-6, C-6), 154.45 (C-4).

HRMS (FAB) : found 581.3022, $C_{36}H_{41}N_2O_5$ (M^++H) requires 581.3015.

Attempted dimerisation of dihydrocodeinone (117) with potassium tert-butoxide

To a stirred solution of **117** (306mg, 1.02mmol) in THF (20ml) was added potassium *tert*-butoxide (110mg, 0.98mmol) in one portion. The reaction mixture was stirred at room temperature for 12 hr and then refluxed for further 8 hr. TLC analysis showed no reaction. THF was then removed *in vacuo* and the resultant residue partitioned between water and DCM. The mixture was extracted with DCM (x2), the combined organic extracts dried ($MgSO_4$) and DCM removed under reduced pressure to leave an off white solid. Crystallisation using absolute ethanol afforded a quantitative yield of starting material.

Reaction between 117 and cyclohexyltriphenylphosphonium bromide

A stirred solution of **117** (300mg, 1.00mmol) and cyclohexyltriphenylphosphonium bromide (840mg, 1.98mmol) in THF (25ml) was refluxed for further 13 hr. TLC analysis showed no reaction and dihydrocodeinone was recovered quantitatively.

Reaction of dihydrocodeinone (117) with isopropyl triphenylphosphonium iodide

To a cooled, stirred suspension of isopropyltriphenylphosphonium iodide (1.44g, 3.34mmol) in THF (20ml) was added potassium *tert*-butoxide (0.37g, 3.34mmol) in one portion. After 1 hr, **117** (0.5g, 1.67mmol) was added to the deep orange ylide solution. A colour change to yellow was immediately observed and the mixture was stirred for a further hour at 20°C before being heated under reflux for 13 hr. After cooling, THF was removed *in vacuo* and the residue dissolved in chloroform and then washed three times with water. The organic phase was dried ($MgSO_4$) and chloroform removed under reduced pressure. Purification by column chromatography using $CHCl_3$:MeOH (9:1) and then $CHCl_3$:MeOH:NH_3 (95:5:1) as eluent afforded 143mg of unreacted dihydrocodeinone, 79mg (8%) of **184** and 32mg (3%) of **174.**

Aldolisation product 184

R_f = 0.30 ($CHCl_3$:MeOH:NH_3 = 90:10:1); *m/z* (FAB) : 599.3 (M^++H, 100%); IR (neat) = 3337 (OH), 1722 (C=O), 1673, 1636, 1609 (ArC-C), 1501 (C-N), 1370, 1329, 1272 (ArC-O-CH_3), 1199, 1153, 1052, 920, 794 cm^{-1}.

δ_H (400MHz) : 1.09-1.23 (3H, m, 3x H-8), 1.45 (1H, br. d, J_{gem} = 13.7Hz, H-7_{eq}), 1.54 (1H, m, J_{gem} = 12.2Hz, H-15_{eq}), 1.69 (1H, m, J_{gem} = 12.2Hz, H-7_{ax}), 1.78 (1H, m, J_{gem} = 12.7Hz, H-15_{eq}), 1.89 (1H, m, J_{gem} = 12.2Hz and $J_{15,16}$= 4.9Hz H-15_{ax}), 2.06 (1H, m, J_{gem} = 12.2Hz and J = 4.9Hz, H-15_{ax}), 2.13-2.29 (5H, m, H-8, H-10_{α}, H-14, 2x H-16_{eq}), 2.35 (1H, dd, J_{gem} = 18.1Hz and $J10_{\alpha,9}$ = 5.4Hz, H-10_{α}), 2.38 (3H, s, N-C<u>H</u>$_3$), 2.40 (3H, s, N-C<u>H</u>$_3$), 2.48 (1H, m, J_{gem} = 12.2Hz and J = 3.9Hz, H-16_{ax}), 2.54 (1H, m, J_{gem} = 12.2Hz and J = 3.9Hz, H-16_{ax}), 2.61 (1H, m, J_{gem} = 12.2Hz and J = 2.9Hz, H-14), 2.77 (1H, dd, J_{gem} = 12.7Hz and J = 2.9Hz, H-7), 2.98 (1H, d, J_{gem} = 18.1Hz, H-10_{β}), 3.00 (1H, d, J_{gem} = 18.6Hz, H-10_{β}), 3.05 (1H, br. s, H-9), 3.15 (1H, m, $J_{9,14}$ = 2.4Hz, H-9), 3.86 (3H, s, O-C<u>H</u>$_3$), 3.93 (3H, s, O-C<u>H</u>$_3$), 4.56 (1H, s, H-5), 4.68 (1H, s, H-5), 6.62 (2H, d, $J_{1,2}$ = 8.3Hz, 2x H-1), 6.69 (1H, d, $J_{2,1}$ = 8.3Hz, H-2), 6.71 (1H, d, $J_{2,1}$ = 8.3Hz, H-2).

δ_C (400MHz) : 19.73 (C-8), 20.12 and 20.15 (C-10), 26.74 (C-8), 29.76 (C-7), 35.41 and 36.98 (C-15), 42.61 (C-14), 42.70 and 42.87 (N-<u>C</u>H$_3$), 42.92 (C-14), 43.01 (C-13), 46.85 and 47.20 (C-16), 48.32 (C-13), 56.16 and 56.86 (O-<u>C</u>H$_3$), 57.13 (C-7), 59.03 and 59.66 (C-9), 72.82 (C-6), 91.70 and 92.79 (C-5), 112.56 and 114.79 (C-2), 119.29 and 119.81 (C-1), 126.35 and 126.35 (C-11), 127.10 and 130.34 (C-12), 141.44 and 142.81 (C-3), 145.23 and 145.30 (C-4), 208.34 (C-6).

HRMS (FAB) : found 599.3152, $C_{36}H_{43}N_2O_6$ (M^++H) requires 599.3121.

Preparation of Robinson annulation product 193

a) using 1N NaOH[105]

To a stirred, cooled solution of dihydrocodeinone (**117**) hydrochloride (0.5g, 1.49mmol) and 1N NaOH (5.96ml, 5.96mmol) in methanol (10ml) was added MVK (0.29ml, 3.42mmol) dropwise. After the mixture had been stirred at room temperature for 14 hr under nitrogen, additional MVK (0.09ml, 1.03mmol) was added. The mixture was stirred for a further 2 hr and then made neutral by the addition of aqueous 10% HCl. The resulting mixture was concentrated and extracted with $CHCl_3$ (x3). The combined chloroform extracts were washed with brine, dried ($MgSO_4$), and the solvent removed under reduced pressure to give a brown oily residue. TLC analysis of the residue showed the presence of 4 new components which could not be separated by column chromatography. Analysis of the reaction mixture by mass spectrometry revealed a mass ion peak at *m/z*=352, consistant with **193**.

(b) using ethanolic sodium ethoxide[106]

A solution of ethanolic sodium ethoxide (9mg, 0.37mmol of sodium in 1ml EtOH) was added to an efficiently stirred solution of **117** (506mg, 1.68mmol) in ethanol (12ml) maintained at -10°C. The reaction was left stirring for a further 0.5 hr before MVK (0.17ml, 0.17mmol) was added dropwise to the mixture. After 20 hr, the reaction mixture was washed with saturated sodium chloride solution, water and then extracted with DCM. Evaporation of solvent after drying ($MgSO_4$) afforded a white solid. Purification by column chromatography using $CHCl_3$:MeOH:NH_3 (98:1:1) as eluent afforded the title compound (25mg, 4%) as a colourless oil.

(c) using sodium hydride

To a stirred solution of **117** (102mg, 0.34mmol) in dry THF (5ml) at 0°C was added NaH (10mg, 0.34mmol). The mixture was stirred for 1 hr before MVK (0.03ml,

0.34mmol) was added. TLC analysis of the reaction mixture after 24 hr showed little conversion to the desired compound and attempted separation of the components by column chromatography using $CHCl_3$:MeOH:NH_3 (98:1:1) as eluent was unsuccessful.

(d) using potassium tert-butoxide[107]

To a cooled solution of **117** (138mg, 0.46mmol) in dry THF (15ml) was added potassium *tert*-butoxide (52mg, 0.46mmol). The reaction was stirred for a further 0.5 hr before MVK (0.04ml, 0.46mmol) was added. TLC analysis of the reaction mixture after 24 hr showed the presence of mainly unreacted **117** plus 4 different components. Attempted separation of the components by column chromatography using $CHCl_3$:MeOH:NH_3 (98:1:1) as eluent was unsuccessful.

(e) using lithium diisopropylamide [108]

To a stirred solution of **117** (257mg, 0.86mmol) in THF (10ml) at -78°C was added lithium diisopropylamide (0.43ml, 0.86mmol). The mixture was stirred for a further hour before MVK (0.07ml, 0.86mmol) was added. TLC analysis of the reaction mixture after 24 hr showed mainly unreacted starting material and also the presence of 4 other components. THF was removed *in vacuo* and the resultant residue partitioned between water and chloroform. The organic layer was collected and the aqueous fraction extracted with $CHCl_3$ (x2). The combined chloroform layers were dried ($MgSO_4$) and chloroform removed under reduced pressure. Purification by column chromatography using $CHCl_3$:MeOH:NH_3 (98:1:1) as eluent afforded **193** (10mg, 3%) as a colourless oil.

Robinson annulation product 193β

Rf = 0.42 ($CHCl_3$:CH_3OH:NH_3 = 9:1:0.1); *m/z* (FAB) : 352.1 (M^++H, 100%); IR (neat) = 1711 (C=O), 1636 (ArC-C), 1608, 1501 (C-N), 1446, 1372, 1334, 1278 (ArC-O-CH_3), 1258, 1215, 1155, 1108, 1054 cm^{-1}.

δ_H (270MHz) : 1.25 (1H, ddd, J_{gem} = 13.8Hz, $J_{8ax,7}$ = 13.8Hz and $J_{8ax,14}$ = 10.8Hz, H-8_{ax}), 1.25 (1H, m, J_{gem} = 13.8Hz and $J_{8eq,14}$ = 7.7Hz, H-8_{eq}), 1.63 (1H, m, H-22ax), 1.82 (1H, m, J_{gem} = 12.1Hz and $J_{15eq,16ax}$ = 3.8Hz, H-15_{eq}), 1.94 (1H, m, J_{gem} = 12.1Hz and $J_{15ax,16eq}$ = 5.1Hz, H-15_{ax}), 1.98 (1H, m, H-22eq), 2.15 (1H, ddd, $J_{14,8ax}$ = 10.8Hz, $J_{14,8eq}$ = 7.7Hz and $J_{14,9}$ = 2.7Hz, H-14), 2.21-2.45 (4H, m, H-7, H-16_{ax}, H-21_{ax}, H-21_{eq}), 2.40 (3H, s, N-C<u>H</u>$_3$), 2.43 (1H, dd, J_{gem} = 18.7Hz and $J_{10\alpha,9}$ = 6.2Hz, H-10α), 2.53 (1H, dd, J_{gem} = 12.3Hz and $J_{16,15ax}$ = 4.1Hz, H-16_{eq}), 3.05 (1H, d, J_{gem} = 18.7Hz, H-10β), 3.13 (1H, dd, $J_{9,10\alpha}$ = 6.2Hz and $J_{9,14}$ = 2.7Hz, H-9), 3.86 (3H, s, O-C<u>H</u>$_3$), 4.90 (1H, s, H-5), 6.09 (1H, d, J = 1.7Hz, C^6=C<u>H</u>), 6.67 (1H, d, $J_{1,2}$ = 8.2Hz, H-1), 6.77 (1H, d, $J_{2,1}$ = 8.2Hz, H-2).

δ_C (400MHz): 19.92 (C-10), 27.69 (C-7), 28.61 (C-22), 29.05 (C-8), 34.88 (C-21), 37.43 (C-14), 37.43 (C-15), 43.04 (N-<u>C</u>H_3), 44.56 (C-13), 45.78 (C-16), 56.30 (O-<u>C</u>H_3), 59.32 (C-9), 93.39 (C-5), 113.41 (C-2), 119.30 (C-1), 127.71 (C-11), 128.77 (C^6=<u>C</u>H), 129.76 (C-12), 141.89 (C-3), 146.00 (C-4), 158.32 (C-6), 199.51 (C=O).

HRMS (FAB) : found 352.1905, $C_{22}H_{26}NO_3$ (M^++H) requires 352.1913.

Preparation of 6-[(tert-butyldimethylsilyl)oxy]-6,7-didehydro-4,5α-epoxy-3-hydroxy-17-methylmorphinan (206)

(a) using sec-butyllithium as base

To a stirred solution of **117** (941mg, 3.14mmol) in THF (20ml) at -78°C was added *sec*-butyllithium (3.05ml, 3.77mmol). After 1 hr of stirring at the above temperature,

tert-butyldimethylsilyl chloride (574mg, 3.81mmol) was added and the reaction temperature allowed to rise to ambient temperature. After 20 hr, THF was evaporated off under reduced pressure and the residue washed with saturated $NaHCO_3$, water and then extracted with DCM (x3). Column chromatography on silica gel using $CHCl_3$:MeOH (95:5) afforded **206** as a colourless solid (571mg, 44%) and a diastereomeric mixture of **207** (184mg, 16%).

(b) using lithium diisopropylamide as base

Lithium diisopropylamide was prepared by the dropwise addition of *n*-butyllithium (7.54ml, 19mmol) to a solution of diisopropylamine (3.71ml, 28mmol) in dry THF (10ml) at -78°C under an atmosphere of nitrogen. After continuous stirring at -78°C for 1 hr, **117** (5.64g, 18.8mmol), dissolved in dry THF (140ml), was added dropwise to the LDA solution and the mixture stirred for 1 hr at -78°C before *tert*-butyldimethylsilyl chloride was added portionwise . The reaction temperature was then allowed to rise to room temperature. After 19 hr the reaction was quenched with sat. NH_4Cl and THF removed *in vacuo*. The residue was diluted with water and extracted with DCM (x4). The organic phase was dried ($MgSO_4$), evaporated off under reduced pressure and the resultant residue purified by column chromatography using $CHCl_3$:CH_3OH (95:5) as eluent to afford **206** as a colourless solid (5.24g, 67%).

6-[(tert-Butyldimethylsilyl)oxy]-6,7-didehydro-4,5α-epoxy-3-hydroxy-17-methylmorphinan (206)

R_f = 0.71 ($CHCl_3$:MeOH:NH_3 = 90:9:1); Mp. = 91-93°C; *m/z* (FAB) : 414.2 (M^++H, 100%); IR (Nujol) = 1664, 1603 (Ar. C=C), 1497 (C-N), 1444, 1338, 1250, 1207 (C-OMe), 1148, 1039, 1020, 959, 911, 895, 837, 811, 780 cm^{-1}.

δ_H (270MHz) : 0.05 (3H, s, Si-C$\underline{H}_3$), 0.15 (3H, s, Si-C$\underline{H}_3$), 0.94 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 1.58 (1H, m, J_{gem} = 12.5Hz, and $J_{15eq,16ax}$ = 3.9Hz, H-15$_{eq}$), 1.79 (1H, dm, J_{gem} = 12.5Hz, H-8β), 1.89 (1H, dd, J_{gem} = 12.5Hz and $J_{8\alpha,7}$ = 6.6Hz, H-8α), 1.92 (1H, m, J_{gem} = 12.5Hz and $J_{15ax,16eq}$ = 4.8Hz, H-15$_{ax}$), 2.25 (1H, m, J_{gem} = 12.1Hz and $J_{16ax,15eq}$ = 3.9Hz, H-16$_{ax}$), 2.34 (1H, m, $J_{14,9}$ = 2.8Hz, H-14), 2.38 (1H, dd, J_{gem} = 18.7Hz and $J_{10\alpha,9}$ = 5.9Hz, H-10α), 2.41 (3H, s, N-C$\underline{H}_3$), 2.52 (1H, dd, J_{gem} = 12.1Hz and $J_{16eq,15ax}$ = 4.8Hz, H-16$_{eq}$), 3.00 (1H, d, J_{gem} = 18.7Hz, H-10β), 3.12 (1H, dd, $J_{9,10\alpha}$ = 5.7Hz and $J_{9,14}$ = 2.8Hz, H-9), 3.85 (3H, s, O-C$\underline{H}_3$), 4.75 (1H, s, H-5), 4.97 (1H, dd, $J_{7,8\alpha}$ = 6.6Hz and $J_{7,8\beta}$ = 1.8Hz, H-7), 6.60 (1H, d, $J_{1,2}$ = 8.3Hz, H-1), 6.71 (1H, d, $J_{2,1}$ = 8.3Hz, H-2).

δ_C (400MHz): -4.82 (Si-$\underline{C}$H$_3$), -4.69 (Si-$\underline{C}$H$_3$), 18.06 (Si-$\underline{C}$(CH$_3$)$_3$), 20.04 (C-10), 23.95 (C-8), 25.70 (Si-C($\underline{C}$H$_3$)$_3$), 35.63 (C-15), 39.38 (C-14), 42.40 (C-13), 43.08 (N-$\underline{C}$H$_3$), 46.46 (C-16), 56.77 (O-$\underline{C}$H$_3$), 58.99 (C-9), 89.69 (C-5), 109.15 (C-7), 114.09 (C-2), 118.55 (C-1), 127.09 (C-11), 130.86 (C-12), 143.17 (C-3), 145.23 (C-4), 147.57 (C-6).

Found: C, 69.4%; H, 8.60%; N, 3.22%; $C_{24}H_{35}NO_3Si$ requires C, 69.69%; H, 8.53%; N, 3.39%.

6-(sec-Butyl)dihydrocodeine (207)

diastereomer A

R_f = 0. 58 (CHCl$_3$:MeOH:NH$_3$ = 90:9:1); *m/z* (FAB) : 358.2 (M^++H, 100%); IR (neat) = 3428 (OH), 1638, 1610 (ArC-C), 1503 (C-N), 1277 (ArC-O-CH$_3$), 1215 (ArC-O-AlkC) cm^{-1}.

δ_H (270MHz) : 0.92 (3H, s, C$\underline{H}_3$CH$_2$CHCH$_3$), 0.97 (3H, s, CH$_3$CH$_2$CHC$\underline{H}_3$), 0.99-1.45 (4H, m, H-7α, H-7β, H-8α and H-8β), 1.55-1.85 (3H, m CH$_3$C$\underline{H}_2$CHCH$_3$) and (3H, m, CH$_3$CH$_2$C$\underline{H}$CH$_3$), 1.64 (1H, m, J_{gem} = 12.5Hz, H-15$_{eq}$), 1.94 (1H, m, J_{gem}

= 12.5Hz and $J_{15ax,16eq}$ = 4.9Hz, H-15_{ax}), 2.23 (1H, m, H-14), 2.30 (1H, m, J_{gem} = 12.3Hz and $J_{16ax,15eq}$ = 3.9Hz, H-16_{ax}), 2.43 (1H, dd, J_{gem} = 18.5Hz, H-10α), 2.46 (3H, s, N-C<u>H</u>3), 2.63 (1H, dd, J_{gem} = 12.3Hz and $J_{16eq,15ax}$ = 4.9Hz, H-16_{eq}), 3.00 (1H, d, J_{gem} = 18.5Hz, H-10β), 3.18 (1H, m, H-9), 3.86 (3H, s, O-C<u>H</u>3), 4.51 (1H, s, H-5), 6.63 (1H, d, $J_{1,2}$ = 8.3Hz, H-1), 6.70 (1H, d, $J_{2,1}$ = 8.3Hz, H-2).

δ_C (400MHz): 12.52 (CH_3), 12.92 (CH_3), 19.65 (C-8), 19.96 (C-10), 22.59 (C-20), 30.37 (C-15), 36.68 (C-7), 41.91 (C-13), 42.29 (N-<u>C</u>H3), 42.45 (C-14), 44.83 (C-19), 47.06 (C-16), 56.08 (O-<u>C</u>H3), 59.74 (C-9), 74.48 (C-6), 90.97 (C-5), 113.10 (C-2), 118.81 (C-1), 125.30 (C-11), 129.87 (C-12), 144.45 (C-3), 145.34 (C-4).

HRMS (FAB) : found 358.2388, $C_{22}H_{32}NO_3$ (M^++H) requires 358.2382.

diastereomer B

δ_H (270MHz) contains 4.50 (1H, s, H-5).

δ_C (400MHz) contains 19.69 (C-8), 23.56 (C-20), 30.64 (C-15), 36.71 (C-7), 41.94 (C-13), 42.55 (C-14), 45.16 (C-19), 74.39 (C-6), 91.52 (C-5).

Preparation of β-hydroxy ketone 192 from 206

a) using tetrabutylammonium fluoride and methylvinyl ketone

To a stirred solution of **206** (208mg, 0.50mmol) in dry THF (10ml) at -78°C was added MVK (0.04ml, 0.50mmol) and then TBAF (0.50ml, 0.50mmol) dropwise. The mixture was allowed to warm to room temperature and the reaction monitored by TLC. After 4 hr, complete disappearance of starting material was noted and the mixture partitioned with water. THF was then removed under reduced pressure and the aqueous phase extracted with DCM (x3). After drying ($MgSO_4$) and evaporation

of solvent the resultant residue was purified by column chromatography using $CHCl_3$:MeOH (9:1) as eluent to afford **117** (126mg, 84%).

b) using potassium fluoride and methylvinyl ketone

A solution of 'naked' fluoride reagent[112] was prepared by dissolving 18-crown-6 (529mg, 2.00mmol) in dry acetonitrile (10ml) and then adding dry potassium fluoride (141mg, 2.42mmol) [previously dried in an oven at 140°C at atmospheric pressure for 24 hr]. After the heterogeneous system was stirred for 30min, MVK (0.15ml, 1.81mmol) and then **206** (500mg, 1.21mmol) was added. The mixture was stirred efficiently for 29 hr. Acetonitrile was then removed *in vacuo* and the resultant mixture partitioned between water and chloroform. The organic layer was collected and the aqueous layer extracted two times with chloroform. The combined extracts were dried ($MgSO_4$) and removed under reduced pressure. Purification of the resultant residue by column chromatography using $CHCl_3$:MeOH:NH_3 (95:5:1) as eluent afforded 67mg (15%) of **192** as a colourless oil.

β–hydroxy ketone 192

R_f = 0.35 ($CHCl_3$:MeOH:NH_3 = 90:9:1); *m/z* (FAB) : 370.2 (M^++H, 100%), 352.2 (M^++H - H_2O, 18%), 300.2 (M^++H - C_4H_7O, 8%); IR (neat) = 3424 (OH), 1711 (C=O), 1637, 1608 (ArC-C), 1501 (C-N), 1447, 1372, 1278 (ArC-O-CH_3), 1202, 1154, 1108, 1054, 962, 919 cm^{-1}.

δ_H (400MHz) : 1.37-1.46 (1H, m, H-8), 1.50-1.61 (2H, m, H-8 and H-22), 1.67-1.71 (2H, m, H-7 and H-15_{eq}), 1.87 (1H, m, J_{gem} = 12.2Hz and $J_{15ax,16eq}$ = 4.9Hz, H-15_{ax}), 2.01-2.09 (1H, m, H-22), 2.24 (1H, m, J_{gem} = 12.2Hz and $J_{16ax,15eq}$ = 3.4Hz, H-16_{ax}), 2.32 (1H, d, J_{gem} = 13.7Hz, H-21), 2.34-2.49 (2H, m, H-14 and H-19), 2.35 (1H, dd, J_{gem} = 18.6Hz and $J_{10\alpha,9}$ = 5.4Hz, H-10α), 2.41 (3H, s, N-$\underline{CH_3}$), 2.45 (1H, dd, J_{gem} = 13.67Hz and $J_{21,22}$ = 4.9Hz, H-21), 2.53 (1H, dd, J_{gem} = 12.2Hz and $J_{16eq,15eq}$ = 3.9Hz, H-16_{eq}), 2.67 (1H, d, J_{gem} = 14.2Hz, H-19), 3.03

(1H, d, J_{gem} = 18.6Hz, H-10β), 3.14 (1H, dd, $J_{9,10\alpha}$ = 5.4Hz and $J_{9,14}$ = 2.4Hz, H-9), 3.87 (3H, s, O-C<u>H</u>3), 4.22 (1H, s, H-5), 6.68 (1H, d, $J_{1,2}$ = 8.2Hz, H-1), 6.75 (1H, d, $J_{2,1}$ = 8.2Hz, H-2).

δ_C (400MHz): 19.85 (C-10), 24.82 (C-8), 25.65 (C-22), 35.91 (C-7), 37.41 (C-14), 37.83 (C-15), 38.39 (C-21), 42.64 (C-13), 43.22 (N-<u>C</u>H3), 46.83 (C-16), 50.99 (C-19), 56.70 (O-<u>C</u>H3), 59.75 (C-9), 74.81 (C-6), 92.49 (C-5), 113.83 (C-2), 119.93 (C-1), 127.21 (C-11), 130.24 (C-12), 141.96 (C-3), 145.47 (C-4), 208.84 (C=O).

HRMS (FAB) : found 370.2026, $C_{22}H_{28}NO_4$ (M^++H) requires 370.2018.

Attempted preparation of 7-(methyl)dihydrocodeinone (204)

a) from dihydrocodeinone (117)

Dihydrocodeinone (500mg, 1.67mmol) dissolved in THF (15ml) was added dropwise to a stirred solution of lithium diisopropylamide at -78°C (prepared by the addition of *n*-butyl lithium (0.67ml, 1.67mmol) to diisopropylamine (0.33ml, 2.50mmol) in THF (5ml) at -78°C and stirred for 1 hr prior to use). After 1 hr, methyliodide (0.12ml, 2.00mmol) was added dropwise to this mixture and the reaction allowed to warm to room temperature. After 24 hr, TLC analysis showed no depletion of starting material and after removal of THF and subsequent purification by column chromatography, unreacted dihydrocodeinone was recovered.

b) from 206

A solution of 'naked' fluoride reagent was prepared by dissolving 18-crown-6 (529mg, 2.00mmol) in dry acetonitrile (10ml) and then adding dry potassium fluoride (141mg, 2.42mmol). After the heterogeneous system was stirred for 30 min, methyliodide (0.11ml, 1.82mmol) and then **206** (500mg, 1.21mmol) was added. The mixture was stirred efficiently for 24 hr. Acetonitrile was then removed *in vacuo* and

the resultant mixture partitioned between water and chloroform. The organic layer was collected and the aqueous layer extracted two times with chloroform. The combined extracts were dried ($MgSO_4$) and removed under reduced pressure. Purification of the resultant residue by column chromatography using $CHCl_3$:MeOH (9:1) as eluent afforded dihydrocodeinone (344mg, 95%).

Attempted preparation of 7-(allyl)dihydrocodeinone

a) from dihydrocodeinone (117)

Dihydrocodeinone (466mg, 1.56mmol) dissolved in THF (15ml) was added dropwise to a stirred solution of lithium diisopropylamide at -78°C (prepared by the addition of *n*-butyl lithium (0.62ml, 1.56mmol) to diisopropylamine (0.31ml, 2.33mmol) in THF (5ml) at -78°C and stirred for 1 hr prior to use). After 1 hr, allylbromide (0.16ml, 1.87mmol) was added dropwise to this mixture and the reaction allowed to warm to room temperature. After 21 hr, TLC analysis showed no depletion of starting material and after removal of THF and subsequent purification by column chromatography, unreacted dihydrocodeinone was recovered.

b) from 206

A solution of 'naked' fluoride reagent was prepared by dissolving 18-crown-6 (529mg, 2.00mmol) in dry acetonitrile (10ml) and then adding dry potassium fluoride (141mg, 2.42mmol). After the heterogeneous system was stirred for 1hr, allylbromide (0.16ml, 1.82mmol) and then **206** (500mg, 1.21mmol) was added. The mixture was stirred efficiently for 36 hr. Acetonitrile was then removed *in vacuo* and the resultant mixture partitioned between water and chloroform. The organic layer was collected and the aqueous layer extracted two times with chloroform. The combined extracts were dried ($MgSO_4$) and removed under reduced pressure. Purification of the

resultant residue by column chromatography using $CHCl_3$:MeOH (9:1) as eluent afforded dihydrocodeinone (333mg, 92%).

***Preparation of vinyltri-n-butyltin*[115] (212)**

A mixture of tri-*n*-butyltin chloride (4.11ml, 15mmol) and vinylmagnesium bromide [1M solution in THF] (15.24ml, 15mmol) were heated at reflux for 20 hr. After subsequent cooling to room temperature, saturated aqueous NH_4Cl (15ml) was added to the mixture. The organic layer was separated and the residual salts washed with several portions of diethyl ether. The ether layers were combined with the organic layer, dried ($MgSO_4$) and then removed under reduced pressure. The residue was distilled under diminished pressure to afford the title compound as a colourless liquid (3.89g, 81%).

Bp. 93°C at 1.5mmHg; IR (neat) : 1459, 1418, 1378, 1341, 1289, 1249, 1072, 1004, 941, 870cm^{-1}.

δ_H (270Mz) : 0.89-0.96 (15H, m, J = 7.3Hz), 1.27-1.41 (6H, m, J = 7.3Hz), 1.49-1.61 (6H, m, J = 8.3Hz), 5.68 (1H, dd, J_{trans} = 20.7Hz and J_{gem} = 3.7Hz, $C\underline{H}_2$=CHSnBu3), 6.16 (1H, dd, J_{cis} = 14.1Hz and J_{gem} = 3.7Hz, $C\underline{H}_2$=CHSnBu3), 6.48 (1H, dd, J_{trans} = 20.7Hz and J_{cis} = 14.1Hz, CH_2=$C\underline{H}$SnBu3).

δ_C (400MHz) : 9.32 (CH_2=CHSn$(CH_2)_2\underline{C}H_2CH_3$), 13.69 ($CH_2$=CHSn$(CH_2)_2CH_2\underline{C}H_3$), 27.35 ($CH_2$=CHSn$CH_2\underline{C}H_2CH_2CH_3$), 29.16 ($CH_2$=CHSn$\underline{C}H_2(CH_2)_2CH_3$), 133.62 ($\underline{C}H_2$=CHSn$(CH_2)_3CH_3$), 139.03 ($CH_2$=$C\underline{H}Sn(CH_2)_3CH_3$).

Found: C, 52.70; H, 9.53%. $C_{14}H_{30}Sn$ requires: C, 53.03; H, 9.54%.

Preparation of codeine triflate (211)

Dihydrocodeinone (1.00g, 3.34mmol) dissolved in dry THF (22ml) was added to a solution of lithium diisopropylamide (LDA) at -78°C. LDA was freshly prepared by the dropwise addition of *n*-butyl lithium (1.47ml, 3.67mmol) to diisopropylamine (0.27ml, 3.67mmol) dissolved in THF (1ml) and stirred at -78°C for 1.5 hr prior to use. After a further 2 hr at -78°C, a solution of *N*-phenyltrifluoromethanesulphonimide[114] (1.32g, 3.67mmol) in THF (6ml) was added over 15 min and the reaction temperature allowed to warm to room temperature. The mixture was stirred for a further 17 hr before the solvent was removed. The resultant yellow oil was purified by column chromatography on silica gel using $CHCl_3$:MeOH (95:5) as eluent to afford the title compound as a colourless oil (853mg, 59%).

R_f = 0.50 ($CHCl_3$:MeOH = 9:1); *m/z* (FAB) = 432.1 (M^++H, 100%); IR (neat) : 1636 (C=C), 1606 (ArC-C), 1501 (C-N), 1417, 1279 (ArC-O-CH_3), 1221, 1144, 1055, 1030, 955, 913, 884, 848, 795, 755, 608 cm^{-1}.

δ_H (270Mz) : 1.70 (1H, m, J_{gem} = 17.6Hz, $J_{8ax,14}$ = 11.4Hz and $J_{8ax,7}$ = 2.0Hz, H-8_{ax}), 1.78 (1H, m, J_{gem} = 12.1Hz, H-15_{eq}), 1.95 (1H, m, J_{gem} = 12.1Hz and $J_{15ax,16eq}$ = 5.0Hz, H-15_{ax}), 2.13 (1H, m, J_{gem} = 17.6Hz and $J_{8eq,7}$ = 6.4Hz, H-8_{eq}), 2.24 (1H, m, J_{gem} = 12.1Hz, $J_{16ax,15eq}$ = 3.7Hz, H-16_{ax}), 2.40 (1H, dd, J_{gem} = 18.7Hz and $J_{10\alpha,9}$ = 6.0Hz, H-10_{α}), 2.40 (3H, s, N-$C\underline{H}_3$), 2.38 - 2.50 (1H, m, H-14), 2.53 (1H, dd, J_{gem} = 12.1Hz and $J_{16eq,15ax}$ = 3.5Hz, H-16_{eq}), 3.01 (1H, d, J_{gem} = 18.9Hz, H-10β), 3.18 (1H, dd, $J_{9,10\alpha}$ = 5.9Hz and $J_{9,14}$ = 2.8Hz, H-9), 3.83 (3H, s, O-$C\underline{H}_3$), 4.90 (1H, s, H-5), 5.88 (1H, dd, $J_{7,8eq}$= 6.4Hz and $J_{7,8ax}$ = 2.0Hz, H-7), 6.63 (1H, d, $J_{1,2}$ = 8.2Hz, H-1), 6.71 (1H, d, $J_{2,1}$ = 8.2Hz, H-2).

δ_C (400MHz): 19.85 (C-10), 24.31 (C-8), 34.86 (C-15), 37.92 (C-14), 42.66 (N-$\underline{C}H_3$), 43.39 (C-13), 45.97 (C-16), 56.74 (O-$\underline{C}H_3$), 58.38 (C-9), 85.78 (C-5), 114.87 (C-2),

119.65 (C-1), 119.87 (CF3), 123.78 (C-7), 126.25 (C-11), 127.95 (C-12), 143.44 (C-3), 143.97 (C-6), 145.43 (C-4).

HRMS (FAB) : found 432.1083, $C_{19}H_{20}F_3NO_5$ (M^++H) requires 432.1093.

Stille coupling between 211 and vinyltri-n-butyltin[137]

To a mixture of lithium chloride (83mg, 1.96mmol) and tetrakistriphenylphosphine palladium (0) (22mg, 0.02mmol) in dry THF (10ml) under nitrogen was added a solution of codeine triflate (416mg, 0.96mmol) in THF (5ml) and vinyltri-*n*-butyltin (0.29ml, 0.96mmol). The slurry was heated to reflux for 22 hr. After cooling, the solvent was removed *in vacuo* to give a yellow oil. Purification of the crude oil by column chromatography on silica gel using CHCl3:MeOH (95:5) as eluent afforded **210** as a cream coloured solid (270mg, 90%).

Diene 210

R_f = 0.51 (CHCl3:MeOH = 9:1); *m/z* (FAB) = 310.1 (M^++H, 100%); IR (neat) = 1733, 1631 (C=C), 1603 (ArC-C), 1497 (C-N), 1445, 1373, 1334, 1278 (ArC-O-CH3), 1205, 1148, 1103, 1047, 905, 862 cm^{-1}.

δ_H (270Mz) : 1.62 (1H, t, J_{gem} = 13.4Hz, H-8_{ax}), 1.89 (1H, m, J_{gem} = 12.6Hz, H-15_{eq}), 2.00-2.10 (1H, m, H-8_{eq}), 2.07 (1H, m, J_{gem} = 12.5Hz and $J_{15ax,16eq}$ = 4.8Hz, H-15_{ax}), 2.40 (1H, m, J_{gem} = 12.1Hz, $J_{16ax,15eq}$ = 3.7Hz, H-16_{ax}), 2.45-2.55 (1H, m, H-14), 2.51 (3H, s, N-CH3), 2.52 (1H, dd, J_{gem} = 18.9Hz and $J_{10\alpha,9}$ = 6.6Hz, H-10α), 2.69 (1H, dd, J_{gem} = 12.1Hz and $J_{16eq,15ax}$ = 3.9Hz, H-16_{eq}), 3.05 (1H, d, J_{gem} = 18.9Hz, H-10β), 3.27 (1H, dd, $J_{9,10\alpha}$ = 6.4Hz and $J_{9,14}$ = 2.2Hz, H-9), 3.82 (3H, s, O-CH3), 5.10 (1H, d, J_{cis} = 11.0Hz, $C^6CH=CH_2$), 5.24 (1H, s, H-5), 5.53 (1H, d, J_{trans} = 17.6Hz, $C^6CH=CH_2$), 5.85 (1H, dd, $J_{7,8eq}$= 6.4Hz and $J_{7,8ax}$ = 2.2Hz, H-7), 6.22 (1H, dd, J_{trans} = 17.6Hz and J_{cis} = 11.0Hz, $C^6CH=CH_2$), 6.61 (1H, d, $J_{1,2}$ = 8.1Hz, H-1), 6.71 (1H, d, $J_{2,1}$ = 8.3Hz, H-2).

δ_C (400MHz): 20.29 (C-10), 24.92 (C-8), 35.14 (C-15), 38.16 (C-14), 40.99 (C-13), 42.62 (N-$\underline{C}H_3$), 46.77 (C-16), 56.54 (O-$\underline{C}H_3$), 59.21 (C-9), 86.57 (C-5), 113.49 ($C^6CH=\underline{C}H_2$), 114.03 (C-2), 118.48 (C-1), 125.92 (C-11), 128.90 (C-12), 132.10 (C-7), 133.97 (C-6), 136.84 ($C^6\underline{C}H=CH_2$), 143.06 (C-3), 145.05 (C-4).

HRMS (FAB) : found 310.1822, $C_{20}H_{24}NO_2$ (M^++H) requires 310.1807.

Attempted Diels-Alder reaction between 210 and maleic anhydride

a) at room temperature

A mixture of **210** (101mg, 0.33mmol) and maleic anhydride (32mg, 0.33mmol) dissolved in dry DCM (0.2ml), under an atmosphere of nitrogen was stirred at room temperature. TLC analysis of the reaction mixture after 15 hr showed no reaction had taken place and the starting material was recovered after purification by column chromatography.

b) under reflux

A mixture of **210** (101mg, 0.33mmol) and maleic anhydride, (32mg, 0.33mmol), dissolved in dry toluene (2ml), under an atmosphere of nitrogen was heated to reflux for 20 hr. After cooling, the organic solvent was removed and the reaction mixture purified by column chromatography. Starting material was recovered.

c) using aluminium chloride as catalyst

A mixture of **210** (102mg, 0.33mmol), maleic anhydride (32mg, 0.33mmol) and aluminium chloride (45mg, 0.34mmol) dissolved in dry DCM (1ml), was stirred at room temperature and the reaction monitored by TLC. No reaction was observed after 12 hr and starting material was recovered.

The above reaction was repeated using 2 equivalents of aluminium chloride (0.9mg, 0.70mmol), **210** (101mg, 0.33mmol), maleic anhydride (32mg, 0.33mmol) in dry DCM (1ml). Again no reaction was observed by TLC analysis after 16 hr.

d) using 30 equivalents of maleic anhydride

A mixture of maleic anhydride (4.27g, 44mmol) and **210** (450mg, 0.33mmol) under an atmosphere of nitrogen was dissolved in THF (1ml). The solution was warmed to 75°C for 16 hr. After cooling, attempted purification of the resultant black tar by column chromatography using $CHCl_3$:MeOH (9:1) as eluent was unsuccessful and no morphinoid compound could be isolated.

Attempted Diels-Alder reaction of 210 with benzoquinone

A mixture of **210** (341mg, 1.10mmol), benzoquinone (125mg, 1.16mmol) and boron trifluoride etherate (0.14ml, 1.14mmol) was dissolved in dry DCM (1.2ml). The mixture was stirred at room temperature under an atmosphere of nitrogen. After 15 min a brown tar was formed. DCM was then removed *in vacuo*. Attempted purification of the tar by column chromatography on silica gel using $CHCl_3$:MeOH (95:5) was unsuccessful.

Diels-Alder Reaction between 210 and dimethyl acetylenedicarboxylate

a) at room temperature

A mixture of **210** (249mg, 0.81mmol), dimethyl acetylenedicarboxylate (0.1ml, 0.81mmol) was stirred at room temperature for 72 hr. TLC analysis of the mixture showed no reaction and starting material was recovered.

b) using aluminium chloride as Lewis acid catalyst [116]

A mixture of **210** (91mg, 0.29mmol), dimethyl acetylenedicarboxylate (0.04ml, 0.29mmol) and aluminium chloride (43mg, 0.32mmol) in dichloromethane (0.2ml) was stirred at room temperature for 48 hr. TLC analysis of the mixture showed no reaction.

(c) using 30 equivalents of dimethyl acetylenedicarboxylate

210 (450mg, 0.33mmol) under an atmosphere of nitrogen was dissolved in dimethyl acetylenedicarboxylate (4.27g, 44mmol). The solution was warmed to 80°C for 2 hr. After cooling, attempted purification of the resultant black tar by column chromatography using $CHCl_3$:MeOH (95:5) as eluent was unsuccessful and no morphinoid compound could be isolated.

Diels-Alder Reaction between 210 and tetracyanoethylene[138]

A mixture of tetracynanoethylene (78mg, 0.61mmol) and **210** (189mg, 0.61mmol) in dry tetrahydrofuran (1ml) was stirred at room temperature for 24 hr and then heated at reflux for 12 hr. After cooling, removal of solvent under reduced pressure gave a black residue which was purified by column chromatography on silica gel using $CHCl_3$:MeOH (95:5) as eluent. Adduct **223** was obtained as a colourless oil (7mg, 3%).

Adduct 223

R_f = 0.36 ($CHCl_3$:MeOH = 9:1); *m/z* (FAB) = 438.1 (M^++H, 43%).

δ_H (270Mz) : 1.60-1.70 (1H, m), 1.81-2.08 (4H, m), 2.00-2.10 (1H, m, H-8_{eq}), 2.32-2.49 (2H, m), 2.45 (3H, s, N-$C\underline{H}_3$), 2.55-2.66 (1H, m, H-16_{eq}), 2.92-2.99 (1H, m, H-7), 3.09 (1H, d, J_{gem} = 18.9Hz, H-10β), 3.18-3.33 (3H, m), 3.85 (3H, s, O-$C\underline{H}_3$), 4.91

(1H, s, H-5), 6.09-6.14 (1H, m, J = 7.0Hz, C^6=C<u>H</u>CH_2), 6.72 (1H, d, $J_{1,2}$ = 8.2Hz, H-1), 6.81 (1H, d, $J_{2,1}$ = 8.2Hz, H-2).

δ_C (400MHz): 20.08 (C-10), 25.79 (C-8), 32.50 (C-20), 35.17 (C-7), 36.74 (C-14), 36.94 (C-15), 37.33 (<u>C</u>$(CN)_2C(CN)_2$), 42.85 (C-13), 43.00 (N-<u>C</u>H_3), 44.50 (<u>C</u>$(CN)_2C(CN)_2$), 45.90 (C-16), 56.51 (O-<u>C</u>H_3), 58.83 (C-9), 91.90 (C-5), 109.51, 109.98, 110.77, 110.77 (4xCN), 114.39 (C-2), 120.02 (C-1), 123.70 (C^6=<u>C</u>H), 126.92 (C-11), 127.71 (C-12), 131.98 (C-6), 142.26 (C-3), 145.52 (C-4).

HRMS (FAB) : found 438.1916, $C_{26}H_{24}N_5O_2$ (M^++H) requires 438.1930.

Diels-Alder Reaction between 210 and diethyl azodicarboxylate[139]

a) with 1 equivalent of DEAD

A mixture of diethyl azodicarboxylate (0.11ml, 0.71mmol), **210** (221mg, 0.71mmol) in dry toluene (2ml) was heated at reflux for 13 hr under nitrogen. After cooling, removal of solvent under reduced pressure afforded a black residue. Attempted purification of the residue by column chromatography on silica gel using $CHCl_3$:MeOH (97:3) as eluent was unsuccessful and no morphinoid compound could be isolated.

b) with 20 equivalents of DEAD

To **210** (175mg, 0.56mmol), under an atmosphere of nitrogen, was added DEAD (1.78ml, 11mmol). The mixture was warmed to 100°C for 14 hr and then allowed to cool to room temperature. Purification of the reaction mixture by column chromatography on silica gel using EtOAc:Petrol (1:1) as eluent afforded **225** as a colourless oil (38mg, 13%).

Adduct 225

R_f = 0.20 (EtOAc:Petrol = 1:1); *m/z* (FAB) = 541.2 (M^+, 100%), 468.2 (M^+-CO_2Et, 11%); IR (neat) = 1726 (C=O), 1632 (C=C), 1605 (ArC-C), 1501 (C-N), 1420, 1378, 1320, 1281 (ArC-O-CH_3), 1222, 1178, 1126, 1065, 1020 cm^{-1}.

δ_H (270Mz) : 1.00-1.60 (10H, m), 1.80 (4H, br. s), 2.08-2.20 (1H, m), 2.69 (1H, d, J_{gem} = 18.7Hz, H-10β), 2.80-3.00 (1H, m), 3.03-3.11 (1H, m), 3.86 (3H, s, O-$C\underline{H}_3$), 3.95-4.40 (10H, m), 4.87 (1H, s, H-5), 5.95 (1H, d, $C^6C\underline{H}$=CH_2), 6.67 (1H, d, $J_{1,2}$ = 8.2Hz, H-1), 6.80 (1H, d, $J_{2,1}$ = 8.1Hz, H-2).

HRMS (FAB) : found 541.2400, $C_{28}H_{35}N_3O_8$ (M^++H) requires 541.2424.

Diels-Alder reaction between 210 and acrylonitrile

To **210** (125mg, 0.40mmol) was added acrylonitrile (0.80ml, 12mmol) under an atmosphere of nitrogen. The mixture was stirred at 85°C for 14 hr. After cooling, the resultant residue was purified by column chromatography on silica gel using $CHCl_3$:MeOH (97:3) as eluent to afford **231** as a colourless oil (13mg, 9%).

Adduct 231

R_f = 0.48 ($CHCl_3$:CH_3OH = 9:1); *m/z* (FAB) = 363.0 (M^++H, 100%); IR (neat) = 2240 (C≡N), 1631 (C=C), 1603 (ArC-C), 1501 (C-N), 1448, 1371, 1330, 1279 (ArC-O-CH_3), 1205, 1155, 1106, 1055, 909 cm^{-1}.

δ_H (400MHz) : 1.26 (1H, m, J_{gem} = 12.7Hz and J = 10.1Hz, H-20), 1.56 (1H, m, J_{gem} = 12.7Hz and J = 8.7Hz, H-20), 1.66-1.78 (1H, m, H-8), 1.76 (1H, dd, J_{gem} = 12.8Hz, H-15_{eq}), 1.87-1.95 (2H, m, H-8 and H-15_{ax}), 2.03-2.15 (2H, m, H-7 and H-21), 2.17-2.24 (1H, m, H-14 and H-21), 2.32 (1H, m, J_{gem} = 12.2Hz, $J_{16ax,15eq}$ = 3.7Hz, H-16_{ax}), 2.41 (3H, s, N-$C\underline{H}_3$), 2.47 (1H, dd, J_{gem} = 18.5Hz and $J_{10\alpha,9}$ =

6.1Hz, H-10α), 2.52 (1H, dd, J_{gem} = 12.2Hz and $J_{16eq,15ax}$ = 4.3Hz, H-16$_{eq}$), 2.73 (1H, ddd, J = 11.6Hz and J = 5.5Hz, and J = 3.1Hz, H-22), 3.01 (1H, d, J_{gem} = 18.6Hz, H-10β), 3.18 (1H, dd, $J_{9,10\alpha}$ = 6.1Hz and $J_{9,14}$ = 2.4Hz, H-9), 3.86 (3H, s, O-C<u>H</u>$_3$), 4.79 (1H, s, H-5), 5.94 (1H, d, J = 4.9Hz, C^6=C<u>H</u>), 6.64 (1H, d, $J_{1,2}$ = 8.2Hz, H-1), 6.75 (1H, d, $J_{2,1}$ = 8.2Hz, H-2).

δ_C (400MHz): 19.93 (C-10), 21.84 (C-8), 23.85 (C-21), 27.47 (C-7), 27.62 (C-20), 29.96 (C-22), 37.33 (C-14), 37.47 (C-15), 43.12 (N-<u>C</u>H$_3$), 43.64 (C-13), 46.07 (C-16), 56.22 (O-<u>C</u>H$_3$), 59.58 (C-9), 94.82 (C-5), 113.15 (C-2), 119.15 (C-1), 121.03 (C-6), 127.67 (C≡N), 127.87 (C^6=<u>C</u>H), 129.85 (C-11), 133.87 (C-12), 141.75 (C-3), 146.21 (C-4).

HRMS (FAB) : found 363.2083, $C_{23}H_{27}N_2O_2$ (M^++H) requires 363.2073.

Diels-Alder reaction between 210 and methylvinyl ketone

To **210** (102mg, 0.33mmol) was added methylvinyl ketone (0.83ml, 9.93mmol) under an atmosphere of nitrogen. The mixture was heated to reflux for 22 hr. After cooling and subsequent removal of excess methylvinyl ketone *in vacuo*, the resultant residue was purified by column chromatography on silica gel using $CHCl_3$:MeOH (95:5) as eluent to afford **233** as a colourless oil (46mg, 37%).

Adduct 233

R_f = 0.20 ($CHCl_3$:MeOH = 95:5); *m/z* (FAB) = 380.0 (M^++H, 100%), 336.0 (M^++H - C_2H_3O, 10%); IR (neat) = 1707 (C=O), 1630 (C=C), 1603 (ArC-C), 1500 (C-N), 1447, 1358, 1277 (ArC-O-CH_3), 1156, 1106, 1054, 892, 794, 753 cm^{-1}.

δ_H (400MHz) : 0.67-0.76 (1H, m, J_{gem} = 13.2Hz, H-8$_{ax}$), 1.23-1.31 (1H, m, H-8$_{eq}$), 1.46 (1H, m, J_{gem} = 12.7Hz and J = 5.4Hz, H-21$_{ax}$), 1.68 (1H, m, J_{gem} = 13.7Hz and J = 4.7Hz, H-21$_{eq}$), 1.77 (1H, m, J_{gem} = 11.2Hz and $J_{15eq,16ax}$ = 3.4Hz, H-

15_{eq}), 1.81 (3H, s, $C\underline{H}_3C{=}O$), 1.91 (1H, m, J_{gem} = 12.7Hz, $J_{15ax,16eq}$ = 4.9Hz, H-15_{ax}), 1.96-2.04 (1H, m, H-20_{eq}), 2.07-2.26 (3H, m, H-7, H-14, H-20_{ax}), 2.31 (1H, m, J_{gem} = 12.2Hz, $J_{16ax,15eq}$ = 3.4Hz, H-16_{ax}), 2.39 (3H, s, N-$C\underline{H}_3$), 2.40 (1H, dd, J_{gem} = 18.6Hz and $J_{10\alpha,9}$ = 6.3Hz, H-10α), 2.51 (1H, dd, J_{gem} = 12.2Hz and $J_{16eq,15ax}$ = 4.4Hz, H-16_{eq}), 2.60 (1H, m, J = 12.7Hz and J = 4.9Hz, and J = 2.5Hz, H-22), 2.97 (1H, d, J_{gem} = 18.6Hz, H-10β), 3.09 (1H, dd, $J_{9,10\alpha}$ = 6.3Hz and $J_{9,14}$ = 2.9Hz, H-9), 3.88 (3H, s, O-$C\underline{H}_3$), 4.82 (1H, s, H-5), 5.92 (1H, d, J = 4.9Hz, $C^6{=}C\underline{H}$), 6.63 (1H, d, $J_{1,2}$ = 8.3Hz, H-1), 6.71 (1H, d, $J_{2,1}$ = 8.3Hz, H-2).

δ_C (400MHz): 18.50 (C-21), 20.25 (C-10), 24.92 (C-20), 26.14 (C-8), 28.39 (C-7), 28.67 ($\underline{C}H_3C{=}O$), 37.44 (C-14), 37.66 (C-15), 43.35 (N-$\underline{C}H_3$), 43.95 (C-13), 46.13 (C-16), 50.89 (C-22), 56.61 (O-$\underline{C}H_3$), 59.96 (C-9), 95.60 (C-5), 113.59 (C-2), 119.01 (C-1), 127.93 (C-11), 128.66 ($C^6{=}\underline{C}H$), 130.62 (C-12), 135.78 (C-6), 141.96 (C-3), 146.86 (C-4), 210.54 ($CH_3\underline{C}{=}O$).

HRMS (FAB) : found 380.2236, $C_{24}H_{30}NO_3$ (M^++H) requires 380.2226.

Diels-Alder reaction between 210 and methylacrylate

To **210** (115mg, 0.37mmol) was added methylacrylate (1.00ml, 11mmol) under an atmosphere of nitrogen. The mixture was stirred at 90°C for 21 hr. After cooling, the resultant residue was purified by column chromatography on silica gel using $CHCl_3$:MeOH (97:3) as eluent to afford 120mg (82%) of **234** as a 1:1 mixture of isomers.

Adduct 234

R_f = 0.33 ($CHCl_3$:CH_3OH = 97:3); *m/z* (FAB) = 396.1 (M^++H, 100%); IR (neat) = 1731 (C=O), 1631 (C=C), 1603 (ArC-C), 1501 (C-N), 1446, 1371, 1330, 1277 (ArC-O-CH_3), 1196, 1158, 1104, 1053, 1023, 906 cm^{-1}.

δ_H (400MHz) : 0.87 (1H, m, J = 10.3Hz), 1.14 (1H, dd, J = 9.3Hz), 1.37 (1H, m, J = 9.3Hz), 1.53 (1H, m, J = 12.2Hz, J = 5.4Hz), 1.59-1.94 (7H, m), 1.97-2.17 (6H, m, H-7, H-7), 2.21-2.43 (7H, m, H-10α, H-10α, H–14, H–14, H–16, H–16, H–22), 2.39 (3H, s, N-C$\underline{H}_3$), 2.40 (3H, s, N-C$\underline{H}_3$), 2.46-2.58 (3H, m, H-16, H-16, H-22), 2.97 (1H, d, J_{gem} = 18.6Hz, H-10β), 2.99 (1H, d, J_{gem} = 18.6Hz, H-10β), 3.06 (1H, dd, $J_{9,10\alpha}$ = 6.4Hz and $J_{9,14}$ = 2.4Hz, H-9), 3.09 (1H, dd, $J_{9,10\alpha}$ = 6.4Hz and $J_{9,14}$ = 2.4Hz, H-9), 3.54 (3H, s, $CO_2C\underline{H}_3$), 3.60 (3H, s, $CO_2C\underline{H}_3$), 3.86 (3H, s, O-C$\underline{H}_3$), 3.87 (3H, s, O-C$\underline{H}_3$), 4.79 (1H, s, H-5), 4.80 (1H, s, H-5), 5.91 (1H, d, J = 4.9Hz, C^6=C$\underline{H}$), 5.95 (1H, d, J = 2.4Hz, C^6=C$\underline{H}$), 6.59 (1H, d, $J_{1,2}$ = 8.3Hz, H-1), 6.60 (1H, d, $J_{1,2}$ = 8.3Hz, H-1), 6.73 (1H, d, $J_{2,1}$ = 8.3Hz, H-2), 6.74 (1H, d, $J_{2,1}$ = 8.3Hz, H-2).

δ_C (400MHz): 19.42 (CH_2), 19.93 and 20.17 (C-10), 24.41, 24.58, 24.73, 26.24 (CH_2), 28.09 (C-14), 28.97 (CH_2), 29.59 (C-14), 37.36 (C-15), 37.45 and 37.49 (C-7), 37.64 (C-15), 42.59 (C-13), 42.85 (C-22), 43.12 (N-$\underline{C}H_3$), 43.69 (C-13), 46.10 and 46.23 (C-16), 47.79 (C-22), 51.30 and 51.65 ($CO_2\underline{C}H_3$), 56.31 and 56.42 (O-$\underline{C}H_3$), 59.53 and 59.73 (C-9), 95.34 and 95.61 (C-5), 113.31 and 113.31 (C-2), 118.60 and 118.65 (C-1), 127.71 and 127.87 (C-11), 128.07 (C^6=$\underline{C}$H), 129.61 and 130.19 (C-12), 130.36 (C^6=$\underline{C}$H), 134.00 and 135.39 (C-6), 141.66 and 141.81 (C-3), 146.49 and 146.60 (C-4), 174.61 and 175.64 ($\underline{C}O_2CH_3$).

HRMS (FAB) : found 396.2179, $C_{24}H_{30}NO_4$ (M^++H) requires 396.2175.

Attempted Diels-Alder reaction between 210 and thebaine

A stirred mixture of thebaine (103mg, 0.33mmol) and **210** (102mg, 0.33mmol) dissolved in toluene (3ml) was warmed to 50°C. The reaction was monitored by TLC and after 10 hr the mixture cooled and toluene removed under reduced pressure. Purification of the resultant residue by column chromatography using $CHCl_3$:MeOH (95:5) proved unsuccessful. The mixture was subsequently analysed using mass spectrometry which showed the presence of both starting materials.

Preparation of 6β-O-(phenyl)codeine (239)[124, 125]

To a stirred solution of codeine (503mg, 1.68mmol) in THF (10ml) was added diethyl azodicarboxylate (0.40ml, 2.52mmol). The reaction mixture was cooled to 0°C before PPh_3 (671mg, 2.56mmol) and then phenol (0.5g, 1.67mmol) added. The reaction mixture was allowed to warm to room temperature and stirred for a further 24 hr. THF was then evaporated off under reduced pressure and the resultant residue purified by column chromatography on silica gel using $CHCl_3$:MeOH (95:5) as eluent to give the title compound (110mg, 17%) as a colourless oil.

Rf = 0.45 ($CHCl_3$:CH_3OH = 9:1); *m/z* (FAB) : 376.2 (M^++H, 42%), 282.1 (M^++H-C_6H_5O, 8%); IR (neat) = 1729, 1636, 1595, 1497 (C-N), 1448, 1374, 1339, 1278 (ArC-O-CH_3), 1226, 1156, 1052 cm^{-1}.

δ_H (270MHz) : 1.70 (1H, d, J_{gem} = 12.3Hz, H-15eq), 2.12 (1H, m, J_{gem} = 12.3Hz and $J_{15ax,16eq}$ = 5.0Hz, H-15_{ax}), 2.36 (1H, dd, J_{gem} = 18.7Hz and $J_{10\alpha,9}$ = 5.5Hz, H-10α), 2.39 (1H, m, $J_{16ax,15ax}$ = 12.5Hz, J_{gem} = 12.1Hz and $J_{16ax,15eq}$ = 3.7Hz, H-16_{ax}), 2.45 (3H, s, N-C<u>H</u>3), 2.60 (1H, dd, J_{gem} = 12.1Hz and $J_{16,15ax}$ = 4.3Hz, H-16_{eq}), 3.08 (1H, d, J_{gem} = 18.7Hz, H-10β), 3.18 (1H, dd, $J_{14,9}$ = 3.3Hz, H-14), 3.37 (1H, dd, $J_{9,10\alpha}$ = 5.5Hz and $J_{9,14}$ = 3.3Hz, H-9), 3.88 (3H, s, O-C<u>H</u>3), 4.81 (1H, d, $J_{6,7}$ = 5.7Hz, H-6), 4.92 (1H, d, $J_{5,6}$ = 0.7Hz, H-5), 5.75 (1H, dd, $J_{8,7}$ = 9.8Hz and $J_{8,14}$ = 2.0Hz, H-8), 5.96-6.03 (1H, m, $J_{7,8}$ = 9.8Hz and $J_{7,6}$ = 5.5Hz, H-7), 6.59 (1H, d, $J_{1,2}$ = 8.2Hz, H-1), 6.71 (1H, d, $J_{2,1}$ = 8.2Hz, H-2), 6.77 (1H, d, *J* = 8.8Hz, *p*-ArC<u>H</u>), 6.95 (1H, d, $J_{m,o}$ = 7.3Hz, *m*-ArC<u>H</u>), 6.98 (1H, d, *J* = 8.3Hz, *m*-ArC<u>H</u>), 7.28 (1H, d, $J_{m,o}$ =7.3Hz, *m*-ArC<u>H</u>), 7.29 (1H, d, $J_{m,o}$ =7.3Hz, *m*-ArC<u>H</u>).

δ_C (400MHz): 20.20 (C-10), 35.67 (C-15), 39.88 (C-14), 42.97 (N-CH_3), 44.17 (C-13), 46.79 (C-16), 56.32 (O-CH_3), 58.84 (C-9), 72.36 (C-6), 91.12 (C-5), 112.86 (C-2), 115.75 (2x*m*-ArCH), 119.01 (C-1), 121.11 (2x*p*-ArCH), 127.15 (C-11), 127.69 (C-

7), 129.54 (2x*o*-ArCH), 130.47 (C-12), 135.38 (C-8), 142.03 (C-3), 145.73 (C-4), 156.99 (*i*-ArCH).

HRMS (FAB) : found 376.1913, $C_{24}H_{26}NO_3$ (M^++H) requires 376.1913.

Preparation of 6β-O-(2-bromophenyl)codeine (88)

To a cooled, stirred solution of codeine (0.50g, 1.67mmol), PPh_3 (0.88g, 3.34mmol) and 2-bromophenol (0.39ml, 3.34mmol) in THF (10ml) was added diethyl azodicarboxylate (0.53ml, 3.34mmol) dropwise. The reaction mixture was allowed to warm to room temperature and stirred for a further 22 hr. The reaction mixture was evaporated to dryness and the residue dissolved in a 10% solution of tartaric acid (30ml). The solution was washed with ethyl acetate (x3), made alkaline with conc. NH_4OH (pH 10) and then extracted with $CHCl_3$ (x3). The chloroform layer was dried ($MgSO_4$) and after removal of solvent, the resultant residue purified by column chromatography on silica gel using $CHCl_3$:MeOH (95:5) as eluent to give the title compound as a colourless oil (312mg, 41%).

Rf = 0.39 ($CHCl_3$:CH_3OH = 95:5); *m/z* (FAB) : 453.8 (M^++H, 59%), 281.9 (M^++H-C_6H_4OBr, 90%); IR (neat) = 1728, 1635, 1599, 1582, 1502 (C-N), 1471, 1446, 1340, 1277 (ArC-O-CH_3), 1239, 1155, 1115, 1048, 973, 947, 909 cm^{-1}.

δ_H (400MHz) : 1.84 (1H, m, J_{gem} = 12.2Hz, H-15eq), 2.19 (1H, m, $J_{15ax,16ax}$ = 12.7Hz, J_{gem} = 12.2Hz and $J_{15ax,16eq}$ = 5.4Hz, H-15ax), 2.35 (1H, dd, J_{gem} = 18.6Hz and $J_{10\alpha,9}$ = 5.9Hz, H-10α), 2.40 (1H, m, $J_{16ax,15ax}$ = 12.7Hz, J_{gem} = 12.2Hz and $J_{16ax,15eq}$ = 3.4Hz, H-16ax), 2.46 (3H, s, N-C<u>H</u>3), 2.60 (1H, dd, J_{gem} = 12.2Hz and $J_{16eq,15ax}$ = 3.9Hz, H-16eq), 3.08 (1H, d, J_{gem} = 18.6Hz, H-10β), 3.28 (1H, dd, $J_{14,9}$ = 3.4Hz and $J_{14,8}$ = 2.0Hz, H-14), 3.37 (1H, dd, $J_{9,10\alpha}$ = 5.9Hz and $J_{9,14}$ = 3.4Hz, H-9), 3.86 (3H, s, O-C<u>H</u>3), 4.87 (1H, d, $J_{6,7}$ = 5.8Hz, H-6), 4.95 (1H, s, H-5), 5.79 (1H, dd, $J_{8,7}$ = 9.8Hz and $J_{8,14}$ = 2.0Hz, H-8), 5.99-6.04 (1H, m, $J_{7,8}$ =

9.8Hz, $J_{7,6}$ = 5.9Hz and $J_{7,14}$ = 1.0Hz, H-7), 6.59 (1H, d, $J_{1,2}$ = 8.3Hz, H-1), 6.69 (1H, d, $J_{2,1}$ = 8.3Hz, H-2), 6.85 (1H, ddd, $J_{4',3'}$ = 7.8Hz, $J_{4',5'}$ = 7.3Hz and J = 1.5Hz, H-4'), 7.06 (1H, dd, $J_{6',5'}$ = 8.3Hz and J = 1.5Hz, H-6'), 7.25 (1H, ddd, $J_{5',6'}$ = 8.3Hz, $J_{5',4'}$ = 7.3Hz and J = 1.5Hz, H-5'), 7.55 (1H, dd, $J_{3',4'}$ = 7.8Hz and J = 1.5Hz, H-3').

δ_C (400MHz): 20.33 (C-10), 35.78 (C-15), 39.95 (C-14), 43.11 (N-CH_3), 44.37 (C-13), 46.81 (C-16), 56.26 (O-CH_3), 58.86 (C-9), 73.56 (C-6), 91.17 (C-5), 112.70 (C-2), 113.67 (C-2'), 115.64 (C-6'), 119.04 (C-1), 122.57 (C-4'), 127.04 (C-7), 127.37 (C-11), 128.41 (C-5'), 130.44 (C-12), 133.53 (C-3'), 136.78 (C-8), 141.94 (C-3), 146.15 (C-4), 153.44 (1').

HRMS (FAB) : found 454.1005, $C_{24}H_{25}NO_3Br$ (M^++H) requires 454.1018.

Radical coupling of 88[129, 130]

To a stirred solution of **88** (100mg, 0.23mmol) in dry toluene (1ml) under nitrogen was added tri-*n*-butyltin hydride (0.08ml, 0.30mmol). The mixture was warmed to 50°C before a catalytic amount of AIBN was added. The temperature was raised to reflux for 20 hr. After cooling, toluene was removed *in vacuo*, the resultant residue dissolved in EtOAc and the organic layer washed (x2) with a 10% aqueous solution of tartaric acid. The combined aqueous extracts were made alkaline (pH 9) with conc. NH_4OH and then extracted with chloroform (x3). The combined chloroform layers were dried ($MgSO_4$) and removal of solvent afforded **82** as a colourless oil (78mg, 90%).

6β,7β-(2',3'-Dihydrobenzofuran)deoxycodeine (82)

Rf = 0.30 ($CHCl_3$:CH_3OH = 95:5); *m/z* (FAB) : 376.2 (M^++H, 100%); IR (neat) = 1731, 1633, 1601, 1501 (C-N), 1448, 1370, 1334, 1275 (ArC-O-CH_3), 1218, 1155, 1111, 1052, 930 cm^{-1}.

δ_H (400MHz) : 1.20-1.29 (1H, m, $J_{8ax,14}$ = 13.7Hz, J_{gem} = 12.2Hz and $J_{8,7}$ = 7.3Hz H-8ax), 1.62 (1H, ddd, J_{gem} = 12.2Hz, $J_{8eq,14}$ = 3.4Hz, and $J_{8eq,7}$ = 2.9Hz, H-8eq), 1.69 (1H, m, J_{gem} = 12.2Hz and $J_{15eq,16ax}$ = 3.4Hz, H-15eq), 1.83 (1H, m, $J_{15ax,16ax}$ = 13.7Hz, J_{gem} = 12.2Hz and $J_{15ax,16eq}$ = 5.4Hz, H-15ax), 2.12 (1H, dt, $J_{14,8ax}$ = 13.7Hz, $J_{14,8eq}$ = 3.4Hz and $J_{14,9}$ = 2.9Hz, H-14), 2.27 (1H, m, J_{gem} = 12.2Hz and $J_{16ax,15eq}$ = 3.4Hz, H-16ax), 2.31 (1H, dd, J_{gem} = 19.1Hz and $J_{10\alpha,9}$ = 6.4Hz, H-10α), 2.34 (3H, s, N-CH3), 2.46 (1H, dd, J_{gem} = 12.2Hz and $J_{16eq,15ax}$ = 3.4Hz, H-16eq), 3.01 (1H, dd, $J_{9,10\alpha}$ = 6.4Hz and $J_{9,14}$ = 2.9Hz, H-9), 3.05 (1H, d, J_{gem} = 19.1Hz, H-10β), 3.50 (1H, t, $J_{7,8}$ = 7.3Hz, H-7), 3.90 (3H, s, O-CH3), 4.73 (1H, d, $J_{5,6}$ = 2.0Hz, H-5), 4.83 (1H, dd, $J_{6,7}$ = 9.3Hz and $J_{6,5}$ = 2.0Hz, H-6), 6.65 (1H, d, $J_{1,2}$ = 8.3Hz, H-1), 6.75 (1H, d, $J_{2,1}$ = 8.3Hz, H-2), 6.78 (1H, d, $J_{6',5'}$ = 7.8Hz, H-6'), 6.86 (1H, m, $J_{4',3'}$ = 7.3Hz, $J_{4',6'}$ = 1.0Hz, H-4'), 7.08 (1H, d, $J_{3',4'}$ = 7.3Hz, H-3'), 7.10 (1H, t, $J_{5',6'}$ = 7.8Hz, H-5').

δ_C (400MHz): 19.98 (C-10), 26.07 (C-8), 35.80 (C-7), 37.41 (C-15), 38.23 (C-14), 42.24 (C-13), 42.91 (N-CH3), 46.61 (C-16), 56.43 (O-CH3), 59.28 (C-9), 85.38 (C-6), 92.20 (C-5), 109.48 (C-6'), 113.28 (C-2), 118.98 (C-1), 120.87 (C-4'), 123.65 (C-3'), 127.13 (C-11), 128.19 (C-5'), 129.25 (C-2'), 130.38 (C-12), 142.27 (C-3), 145.34 (C-4), 155.51 (1').

HRMS (FAB) : found 376.1931, $C_{24}H_{26}NO_3$ (M^++H) requires 376.1913.

Attempted coupling between codeine and cyclohexanol (248)

To a stirred solution of cyclohexanol (0.17ml, 1.67mmol) in THF (20ml) was added diethyl azodicarboxylate (0.26ml, 1.67mmol). The reaction mixture was cooled to 0°C and PPh3 (438mg, 1.67mmol) added portionwise. After stirring for 1 hr at room temperature codeine (501mg, 1.67mmol) dissolved in THF (5ml) was added dropwise

over 5 min. The reaction mixture was stirred for 48 hr. TLC analysis showed that no reaction had taken place and codeine was recovered quantitatively.

The above reaction was repeated using cyclohexanol (0.07ml, 0.67mmol) in THF (10ml) and codeine (201mg, 0.67mmol) but 1.5 equivalents of diethyl azodicarboxylate (0.6ml, 1.00mmol) and PPh_3 (264mg, 1.00mmol). No reaction was observed by TLC analysis (48 hr) and codeine was recovered quantitatively.

In a further reaction, diethyl azodicarboxylate (0.79ml, 5.01mmol) was added to a stirred solution of cyclohexanol (0.17ml, 1.67mmol) in THF (20ml) and the mixture cooled to 0°C before PPh_3 (1.31g, 5.01mmol) added in small portions. A colour change to deep orange was observed. After stirring for 1 hr at room temperature codeine (0.5g, 1.67mmol) dissolved in THF (5ml) was added dropwise over 5 min. A colour change to yellow was observed. The reaction mixture was stirred for a further 67 hr before THF was evaporated off under reduced pressure. The resultant residue was purified by column chromatography on silica gel using $CHCl_3$:MeOH:NH_3 (95:5:1) as eluent to afford **245** (85mg, 11%) as a colourless oil and unreacted codeine (343mg).

8β-(1,2-Dicarbethoxyhydrazine)deoxypseudocodeine (245)

R_f = 0.46 ($CHCl_3$:CH_3OH = 9:1); *m/z* (FAB) : 458.1 (M^++H, 62%), 282.1 (M^++H-$C_6H_{11}N_2O_4$, 19%); IR (neat) = 1733, 1709, 1638 (C=C), 1607 (ArC-C), 1502 (C-N), 1447, 1410, 1379, 1325, 1283 (ArC-O-CH_3), 1258, 1223, 1174, 1152, 1123, 1093, 1056, 933, 914, 866 cm^{-1}.

δ_H (270MHz): 1.27 (3H, t, J = 7.0Hz, $CO_2CH_2C\underline{H}_3$), 1.29 (3H, t, J = 7.0Hz, $CO_2CH_2C\underline{H}_3$), 1.73 (1H, d, J_{gem} = 12.5Hz, H-15_{eq}), 2.07 (1H, m, J_{gem} = 12.5Hz, H-15_{ax}), 2.27 (1H, m, J_{gem} = 12.2Hz and $J_{16ax,15eq}$ = 3.2Hz, H-16_{ax}), 2.37 (1H, dd, J_{gem} = 18.3Hz, and $J_{10\alpha,9}$ = 5.7Hz, H-10α), 2.38 (3H, s, N-$C\underline{H}_3$), 2.55 (1H, dd, J_{gem} = 12.2Hz and $J_{16,15ax}$ = 4.1Hz, H-16_{eq}), 2.98 (1H, br. s, H-14), 3.02 (1H, d,

J_{gem} = 18.3Hz, H-10β), 3.27 (1H, dd, $J_{9,10\alpha}$ = 5.7Hz and $J_{9,14}$ = 2.8Hz, H-9), 3.87 (3H, s, O-C<u>H</u>3), 4.10-4.34 (4H, m, $CO_2C\underline{H}_2CH_3$), 4.76 (1H, br. s, H-8), 5.12 (1H, br. s, H-5), 5.68 (2H, s, H-6 and H-7), 6.55 (1H, d, $J_{1,2}$ = 8.1Hz, H-1), 6.68 (1H, d, $J_{2,1}$ = 8.2Hz, H-2), 7.38 (1H, br. s, N<u>H</u>$CO_2CH_2CH_3$).

δ_C (270MHz): 14.43 2(N-$CO_2CH_2\underline{C}H_3$), 20.11 (C-10), 34.74 (C-15), 39.96 (C-14), 42.78 (N-Me), 44.05 (C-13), 47.05 (C-16), 56.66 (O-Me), 59.06 (C-9), 62.05 (N-$CO_2\underline{C}H_2CH_3$), 62.65 (N-$CO_2\underline{C}H_2CH_3$), 77.21 (C-8), 91.52 (C-5), 113.81 (C-2), 118.70 (C-1), 127.15 (C-7), 128.73 (C-11), 130.41 (C-12), 132.63 (C-6), 142.31 (C-3), 145.26 (C-4), 155.43 (N-$\underline{C}O_2CH_2CH_3$), 156.94 (N-$\underline{C}O_2CH_2CH_3$).

HRMS (FAB) : found 458.2326, $C_{24}H_{32}N_3O_6$ (M^++H) requires 458.2291.

Preparation of 2-bromo-cyclohexan-1-ol (249)[133]

A mixture of cyclohexene (5.0g, 0.06mmol), N-bromosuccimide (10.85g, 0.06mmol) and water (25ml) was stirred vigorously at room temperature until the solid NBS had disappeared (45 min). The reaction was left stirring overnight. The bromohydrin layer was separated and the aqueous layer extracted with toluene (x3). Distillation of the combined product gave 8.4g (77%) of the title compound.

Bp. = 86.6-88.4°C (10mm); IR (neat) = 3398 (C-OH); *m/z* (EI) : 178.0 (M^+, 8%), 99.1 (M^+-Br, 75%), 81.1 (M^+ - BrH_2O, 100%).

δ_H (270MHz) : 1.19-1.46 (3H, m), 1.62-1.92 (3H, m), 2.06-2.21 (1H, m), 2.29-2.40 (1H, m), 3.28 (1H, s, O<u>H</u>), 3.57-3.68 (1H, m), 3.86-3.98 (1H, m).

Attempted coupling between codeine and 249

To a stirred solution of 2-bromocyclohexan-1-ol (599mg, 3.35mmol) in THF (15ml) was added DEAD (0.77ml, 4.92mmol) and PPh_3 (1.29g, 4.92mmol). The reaction

mixture was left stirring for 0.5 hr before codeine (982mg, 3.28mmol) in THF (5ml) was cannulated into the reaction vessel. After 41 hr, THF was removed *in vacuo* and the crude mixture purified by column chromatography on silica gel using $CHCl_3$:MeOH (95:5) as eluent to afford 95β (185mg, 16%) and unreacted codeine (468mg).

Attempted preparation of 6β-(2-bromoaniline)codeine (89)[135]

To a cooled, stirred solution of codeine (0.50g, 1.67mmol), PPh_3 (0.88g, 3.34mmol) and 2-bromoaniline (0.57g, 3.34mmol) in THF (10ml) was added diethyl azodicarboxylate (0.53ml, 3.34mmol) dropwise. The reaction mixture was allowed to warm to room temperature and stirred for a 40 hr. THF was then evaporated under reduced pressure and the resultant residue purified by column chromatography on silica gel using $CHCl_3$:MeOH (95:5) as eluent to give **245** (390mg, 51%) as a colourless oil.

CHAPTER 4

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CHAPTER 5

APPENDIX

5.1. X-Ray Crystallography Data for Compound **159**

A crystal of approximate dimensions 0.3 x 0.3 x 0.35 mm was used for data collection.

Crystal data: $C_{24}H_{33}NO_3$, M = 383.51, Orthorhombic , a = 11.135(3), b = 12.087(3), c = 15.464(3) Å, U = 2081.3(9) Å^3, space group $P2_12_12_1$, Z = 4, D_c = 1.224 gcm^{-3}, (μMo-K_α) = 0.080 mm^{-1}, F(000) = 832. Crystallographic measurements were made at 293(2)° K on a CAD4 automatic four-circle diffractometer in the range 2.13<θ<23.90°. Data (3726 reflections) were corrected for Lorentz and polarization but not for absorption.

In the final least squares cycles all atoms were allowed to vibrate anisotropically. Hydrogen atoms were included at calculated positions where relevant.

The solution of the structure (SHELX86)[1] and refinement (SHELX93)[2] converged to a conventional [i.e. based on 1827 with $Fo>4\sigma(Fo)$] $R1$ = 0.0519 and $wR2$ = 0.1279. Goodness of fit = 0.922. The max. and min. residual densities were 0.184 and -0.180eÅ^{-3} respectively. The asymmetric unit (shown in Fig. ...), along with the labelling scheme used was produced using ORTEX.[3] Final fractional atomic co-ordinates and isotropic thermal parameters, bond distances and angles are given in Tables ... , ... and ... respectively. Tables of anisotropic temperature factors are available as supplementary data.

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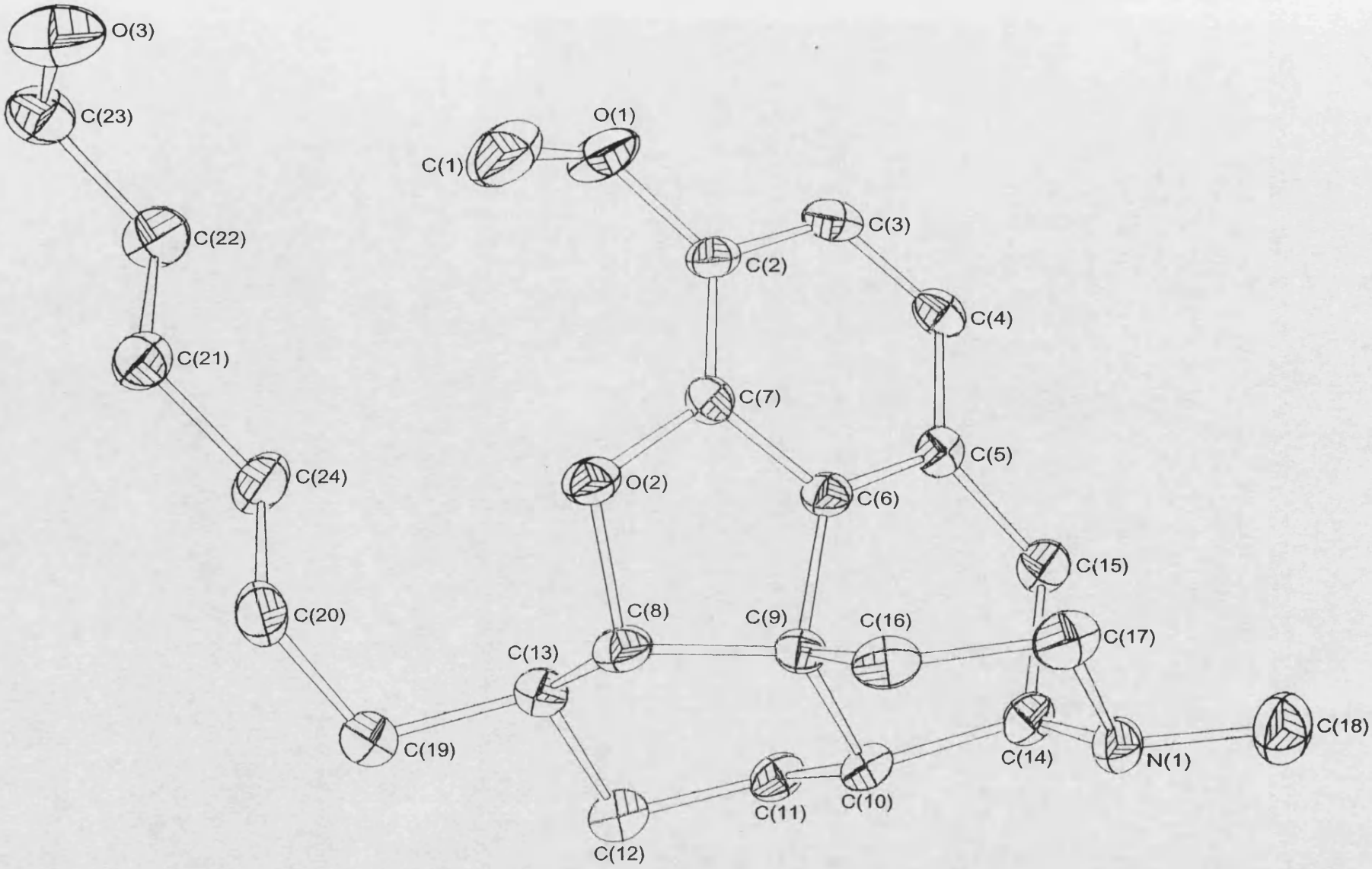


6-(6-Hydroxyhexyl)dihydrodeoxycodeine (159)

Table 1. Crystal data and structure refinement

Empirical formula	$C_{24} H_{33} N O_3$
Formula weight	383.51
Temperature	293(2)°K
Wavelength	0.70930 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 11.135(3)Å
	b = 12.087(3)Å
	c = 15.464(3)Å
Volume	2081.3(9) A3
Z	4
Density (calculated)	1.224 Mg/m^3
Absorption coefficient	0.080 mm^{-1}
F(000)	832
Crystal size	0.3 x 0.3 x 0.35 mm
Theta range for data collection	2.13 to 23.90°
Index ranges	-12<=h<=12; 0<=k<=13; -17<=l<=0
Reflections collected	3726
Independent reflections	3247 [R(int) = 0.0259]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3245 / 0 / 256
Goodness-of-fit on F^2	0.922
Final R indices [$I>2\sigma(I)$]	R1 = 0.0519 wR2 = 0.1279
R indices (all data)	R1 = 0.1417 wR2 = 0.1905
Absolute structure parameter	1(4)
Largest diff. peak and hole	0.184 and -0.180 $eÅ^{-3}$
Weighting scheme	calc $w=1/[\sigma^2(Fo^2)+(0.0927P)^2+2.5829P]$
	where $P=(Fo^2+2Fc^2)/3$
Extinction coefficient	0.0057(16)
Extinction expression	$Fc^*=kFc[1+0.001xFc^2\lambda^3/\sin(2\theta)]^{-1/4}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) . U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
N(1)	-2782(4)	-868(4)	-6422(3)	43(1)
O(1)	-2299(4)	-5159(4)	-3394(3)	71(1)
O(2)	-2329(3)	-4860(3)	-5352(2)	45(1)
O(3)	-1791(4)	-9126(4)	-3251(3)	82(2)
C(1)	-3026(7)	-5984(5)	-3756(5)	80(2)
C(2)	-2153(5)	-4186(5)	-3831(3)	42(1)
C(3)	-1922(5)	-3235(5)	-3354(3)	47(2)
C(4)	-1681(5)	-2221(5)	-3728(3)	43(1)
C(5)	-1695(5)	-2100(4)	-4619(3)	38(1)
C(6)	-1978(5)	-3035(4)	-5086(3)	37(1)
C(7)	-2185(5)	-4058(4)	-4717(3)	38(1)
C(8)	-1836(5)	-4366(4)	-6154(3)	41(1)
C(9)	-2109(5)	-3119(4)	-6052(3)	34(1)
C(10)	-1252(5)	-2292(4)	-6479(3)	37(1)
C(11)	56(5)	-2651(4)	-6383(3)	41(1)
C(12)	212(5)	-3813(5)	-6722(4)	49(2)
C(13)	-500(5)	-4672(4)	-6210(4)	42(1)
C(14)	-1559(5)	-1158(4)	-6116(3)	41(1)
C(15)	-1365(5)	-1070(4)	-5127(3)	45(1)
C(16)	-3401(5)	-2826(5)	-6312(4)	44(1)
C(17)	-3687(5)	-1633(5)	-6073(4)	50(2)
C(18)	-3105(6)	283(5)	-6245(4)	66(2)
C(19)	-307(6)	-5824(5)	-6590(4)	53(2)
C(20)	-814(6)	-6793(5)	-6085(4)	54(2)
C(21)	-640(6)	-7981(5)	-4723(4)	55(2)
C(22)	-137(6)	-8087(5)	-3831(4)	63(2)
C(23)	-525(6)	-9111(6)	-3344(4)	61(2)
C(24)	-240(6)	-6956(5)	-5208(4)	56(2)

Table 3. Bond lengths [Å] and angles [°]

N(1)-C(18)	1.463(7)	C(4)-C(3)-C(2)	123.2(5)
N(1)-C(17)	1.470(7)	C(3)-C(4)-C(5)	120.5(5)
N(1)-C(14)	1.485(7)	C(6)-C(5)-C(4)	116.0(5)
O(1)-C(2)	1.366(6)	C(6)-C(5)-C(15)	117.2(4)
O(1)-C(1)	1.401(8)	C(4)-C(5)-C(15)	126.7(5)
O(2)-C(7)	1.389(6)	C(5)-C(6)-C(7)	123.7(5)
O(2)-C(8)	1.481(6)	C(5)-C(6)-C(9)	126.8(4)
O(3)-C(23)	1.418(7)	C(7)-C(6)-C(9)	109.5(4)
C(2)-C(7)	1.379(7)	C(2)-C(7)-C(6)	120.4(5)
C(2)-C(3)	1.390(8)	C(2)-C(7)-O(2)	128.9(5)
C(3)-C(4)	1.381(8)	C(6)-C(7)-O(2)	110.6(4)
C(4)-C(5)	1.386(7)	O(2)-C(8)-C(13)	108.0(4)
C(5)-C(6)	1.377(7)	O(2)-C(8)-C(9)	103.6(4)
C(5)-C(15)	1.517(7)	C(13)-C(8)-C(9)	115.5(4)
C(6)-C(7)	1.382(7)	C(6)-C(9)-C(10)	108.8(4)
C(6)-C(9)	1.505(7)	C(6)-C(9)-C(16)	109.6(4)
C(8)-C(13)	1.535(8)	C(10)-C(9)-C(16)	108.7(4)
C(8)-C(9)	1.545(7)	C(6)-C(9)-C(8)	98.5(4)
C(9)-C(10)	1.532(7)	C(10)-C(9)-C(8)	118.1(4)
C(9)-C(16)	1.535(7)	C(16)-C(9)-C(8)	112.5(4)
C(10)-C(14)	1.520(7)	C(14)-C(10)-C(11)	115.8(4)
C(10)-C(11)	1.527(7)	C(14)-C(10)-C(9)	106.8(4)
C(11)-C(12)	1.509(7)	C(11)-C(10)-C(9)	111.5(4)
C(12)-C(13)	1.528(7)	C(12)-C(11)-C(10)	109.9(4)
C(13)-C(19)	1.527(8)	C(11)-C(12)-C(13)	113.1(4)
C(14)-C(15)	1.549(7)	C(19)-C(13)-C(12)	110.3(4)
C(16)-C(17)	1.523(7)	C(19)-C(13)-C(8)	112.2(5)
C(19)-C(20)	1.517(8)	C(12)-C(13)-C(8)	111.7(4)
C(20)-C(24)	1.512(8)	N(1)-C(14)-C(10)	107.6(4)
C(21)-C(22)	1.495(8)	N(1)-C(14)-C(15)	115.2(4)
C(21)-C(24)	1.516(7)	C(10)-C(14)-C(15)	113.3(4)
C(22)-C(23)	1.511(9)	C(5)-C(15)-C(14)	114.9(4)
		C(17)-C(16)-C(9)	110.6(4)
C(18)-N(1)-C(17)	111.2(5)	N(1)-C(17)-C(16)	111.3(5)
C(18)-N(1)-C(14)	113.0(5)	C(20)-C(19)-C(13)	116.9(5)
C(17)-N(1)-C(14)	111.3(4)	C(24)-C(20)-C(19)	113.9(5)
C(2)-O(1)-C(1)	118.9(5)	C(22)-C(21)-C(24)	114.6(5)
C(7)-O(2)-C(8)	105.6(4)	C(21)-C(22)-C(23)	115.1(6)
O(1)-C(2)-C(7)	125.8(5)	O(3)-C(23)-C(22)	110.2(6)
O(1)-C(2)-C(3)	118.2(5)	C(20)-C(24)-C(21)	115.2(5)
C(7)-C(2)-C(3)	116.1(5)		

Table 4. Anisotropic displacement parameters (Å x 10^3).
The anisotropic displacement factor exponent takes the form:
$-2\ pi^2\ [\ h2\ a^*\ 2\ U11 + ... + 2\ h\ k\ a^*\ b^*\ U12\ ]$

Atom	U11	U22	U33	U23	U13	U12
N(1)	41(3)	43(3)	45(3)	3(2)	-2(2)	4(2)
O(1)	90(3)	72(3)	50(2)	27(2)	-4(2)	-14(3)
O(2)	55(2)	43(2)	38(2)	4(2)	9(2)	-11(2)
O(3)	68(3)	116(4)	62(3)	15(3)	1(2)	-24(3)
C(1)	99(6)	62(5)	79(5)	18(4)	14(5)	-26(4)
C(2)	36(3)	51(3)	39(3)	13(3)	7(3)	6(3)
C(3)	40(4)	71(4)	30(3)	6(3)	4(3)	7(3)
C(4)	39(3)	54(4)	36(3)	-10(3)	-1(2)	0(3)
C(5)	35(3)	41(3)	38(3)	0(3)	-3(2)	3(3)
C(6)	34(3)	44(3)	33(3)	3(2)	5(2)	1(3)
C(7)	35(3)	40(3)	40(3)	1(3)	6(2)	2(3)
C(8)	46(3)	45(3)	33(3)	5(2)	1(3)	-7(3)
C(9)	35(3)	40(3)	27(3)	-1(2)	1(2)	-3(2)
C(10)	37(3)	41(3)	34(3)	6(2)	2(2)	-6(3)
C(11)	34(3)	46(3)	42(3)	8(3)	1(3)	-3(3)
C(12)	43(3)	57(4)	45(3)	4(3)	2(3)	1(3)
C(13)	44(3)	43(3)	40(3)	0(3)	6(3)	3(3)
C(14)	41(3)	39(3)	44(3)	5(3)	1(3)	-5(3)
C(15)	50(4)	44(3)	42(3)	-2(3)	-13(3)	-2(3)
C(16)	34(3)	58(4)	40(3)	5(3)	0(2)	-7(3)
C(17)	38(3)	65(4)	48(3)	12(3)	0(3)	0(3)
C(18)	71(5)	58(4)	70(4)	1(3)	-10(4)	17(4)
C(19)	62(4)	53(4)	43(4)	-5(3)	7(3)	-1(3)
C(20)	64(4)	41(3)	57(4)	-9(3)	4(3)	0(3)
C(21)	70(4)	47(4)	47(4)	0(3)	-5(3)	-4(3)
C(22)	70(5)	61(4)	57(4)	0(3)	-9(3)	-11(4)
C(23)	64(5)	70(5)	50(4)	-4(3)	-2(3)	-2(4)
C(24)	69(4)	43(4)	56(4)	1(3)	-3(3)	-1(3)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å x 10^3)

Atom	x	y	z	U(eq)
H(3A)	-1993(4)	-9684(4)	-2986(3)	123
H(1A)	-2691(25)	-6217(30)	-4298(17)	120
H(1B)	-3819(14)	-5695(14)	-3850(30)	120
H(1C)	-3067(37)	-6604(18)	-3370(16)	120
H(3)	-1931(5)	-3283(5)	-2753(3)	56
H(4)	-1507(5)	-1615(5)	-3379(3)	52
H(8)	-2264(5)	-4661(4)	-6657(3)	50
H(10)	-1437(5)	-2279(4)	-7098(3)	45
H(11A)	571(5)	-2149(4)	-6702(3)	49
H(11B)	287(5)	-2623(4)	-5779(3)	49
H(12A)	1057(5)	-4006(5)	-6703(4)	58
H(12B)	-42(5)	-3836(5)	-7322(4)	58
H(13)	-181(5)	-4678(4)	-5619(4)	51
H(14)	-1005(5)	-631(4)	-6386(3)	50
H(15A)	-527(5)	-899(4)	-5019(3)	54
H(15B)	-1839(5)	-456(4)	-4910(3)	54
H(16A)	-3499(5)	-2926(5)	-6930(4)	53
H(16B)	-3957(5)	-3318(5)	-6020(4)	53
H(17A)	-4471(5)	-1437(5)	-6298(4)	60
H(17B)	-3714(5)	-1562(5)	-5448(4)	60
H(18A)	-2504(23)	764(5)	-6482(27)	100
H(18B)	-3156(43)	395(11)	-5631(4)	100
H(18C)	-3868(21)	446(12)	-6505(27)	100
H(19A)	-658(6)	-5836(5)	-7164(4)	63
H(19B)	550(6)	-5939(5)	-6657(4)	63
H(20A)	-1670(6)	-6681(5)	-6007(4)	65
H(20B)	-708(6)	-7463(5)	-6422(4)	65
H(21A)	-1510(6)	-7977(5)	-4686(4)	66
H(21B)	-408(6)	-8628(5)	-5055(4)	66
H(22A)	-373(6)	-7442(5)	-3499(4)	75
H(22B)	732(6)	-8085(5)	-3869(4)	75
H(23A)	-265(6)	-9765(6)	-3655(4)	74
H(23B)	-151(6)	-9119(6)	-2777(4)	74
H(24A)	-415(6)	-6313(5)	-4854(4)	67
H(24B)	624(6)	-6989(5)	-5284(4)	67

5.2. Analgesia Data

Effects of subcutaneous administration of various compounds in the hot plate test in the mouse

Group	Subcutaneous treatment	Dose (mg/kg)	Group mean response time (s ± sd) at time (h) post-dose					
			Pre-dose	0.5	1	2	4	6
1	Vehicle	-	11.6 ± 2.67	8.9 ± 1.63	10.1 ± 2.45	7.4 ± 1.14	9.1 ± 2.89	10.6 ± 2.83
2	Codeine (2)	5	9.6 ± 2.00	10.9 ± 0.60	6.4 ± 0.95	10.5 ± 2.70	9.5 ± 1.88	9.5 ± 1.74
3	Dihydrocodeinone (117)	5	10.4 ± 1.59	10.4 ± 2.13	14.1 * ± 2.03	9.2 ± 1.71	8.5 ± 3.32	9.9 ± 2.99
4	125	5	9.7 ± 1.66	8.2 ± 2.40	11.0 ± 0.84	9.2 ± 1.05	8.5 ± 1.54	8.7 ± 1.67
5	138	5	9.9 ± 2.11	10.4 ± 2.54	10.4 ± 1.69	9.0 ± 2.85	11.5 ± 1.86	9.5 ± 1.28
6	126β	5	10.5 ± 2.83	9.9 ± 0.51	10.1 ± 2.34	10.6 ± 1.59	8.7 ± 1.88	8.7 ± 2.15
7	159	5	10.5 ± 3.52	8.2 ± 1.60	12.0 ± 1.23	9.7 ± 4.49	7.2 ± 1.19	11.0 ± 2.04
8	162	5	9.5 ± 2.29	11.1 ± 2.37	8.8 ± 1.98	11.5 ± 2.42	7.8 ± 2.32	7.1 ± 2.83
9	163	5	10.9 ± 1.94	9.4 ± 2.00	11.0 ± 3.23	10.6 ± 1.46	11.1 ± 1.18	9.1 ± 2.06
10	165	5	11.0 ± 2.20	10.2 ± 3.53	9.3 ± 2.60	10.5 ± 2.93	9.3 ± 1.73	9.1 ± 2.95
11	166	5	11.0 ± 2.16	12.7 ± 2.82	10.9 ± 0.75	10.8 ± 1.54	9.4 ± 2.27	9.5 ± 2.87
12	Morphine sulphate	5	11.6 ± 0.48	>21.5 ** ± 4.86	17.9 * ± 5.28	9.7 ± 0.91	10.3 ± 2.88	8.8 ± 1.84

sd Standard deviation

Statistical significance of increased analgesia from pre-dose using ANOVAR: * $p<0.05$, ** $p<0.01$

Individual animal data

Group	Subcutaneous treatment	Dose (mg/kg)	Animal no.	Response time (s) at time (h) post-dose					
				Pre-dose	0.5	1	2	4	6
1	Vehicle	-	1	10.4	7.0	9.5	6.6	6.3	11.5
			2	15.3	9.3	7.1	8.2	8.1	6.4
			3	9.1	10.9	10.6	6.2	8.7	12.7
			4	11.5	8.5	13.0	8.5	13.1	11.7
2	Codeine (2)	5	5	11.9	10.9	6.9	12.5	10.9	11.3
			6	7.5	11.4	7.4	12.1	9.2	7.6
			7	10.5	10.0	5.7	6.6	7.0	8.4
			8	8.4	11.1	5.4	10.8	11.0	10.5
3	Dihydrocodeinone (117)	5	9	8.7	12.0	12.3	9.6	4.8	• 6.8
			10	12.4	7.3	15.1	7.4	6.6	7.9
			11	9.6	10.6	12.4	11.4	10.7	11.6
			12	10.7	11.6	16.4	8.5	11.8	13.1
4	125	5	13	8.3	8.0	10.2	10.0	8.5	10.1
			14	8.7	6.9	12.1	8.4	8.1	9.7
			15	12.0	11.6	11.1	10.1	6.9	6.4
			16	9.6	6.2	10.5	8.1	10.6	8.4
5	138	5	17	9.6	8.9	9.7	7.8	13.0	9.2
			18	12.2	13.9	12.3	13.3	13.2	9.4
			19	7.2	8.2	8.4	7.5	10.1	8.1
			20	10.7	10.5	11.1	7.5	9.7	11.2
6	126β	5	21	9.1	9.7	9.1	12.8	6.3	6.2
			22	7.2	10.6	8.2	9.0	10.1	8.9
			23	13.5	9.5	13.5	10.5	10.3	8.2
			24	12.0	9.6	9.6	10.2	8.1	11.4
7	159	5	25	7.5	6.3	10.4	5.2	7.2	9.9
			26	12.2	7.5	13.2	6.5	7.4	8.6
			27	7.6	8.8	11.6	13.1	5.7	• 12.4
			28	14.6	10.0	12.6	14.0	8.6	12.9
8	162	5	29	6.3	8.0	6.5	8.4	6.9	4.6
			30	9.7	12.8	9.0	14.3	9.3	6.9
			31	10.3	10.5	8.4	11.5	5.0	5.8
			32	11.7	13.1	11.3	11.8	10.1	11.1

Group	Subcutaneous treatment	Dose (mg/kg)	Animal no.	Response time (s) at time (h) post-dose					
				Pre-dose	0.5	1	2	4	6
9	163	5	33	11.4	11.1	7.3	11.0	10.8	6.9
			34	8.0	6.9	9.2	8.8	9.6	7.8
			35	12.2	8.6	14.0	12.3	11.5	11.0
			36	11.9	10.9	13.3	10.3	12.4	10.7
10	165	5	37	9.4	6.7	7.1	7.9	7.0	5.5
			38	11.8	7.7	11.4	12.2	9.0	12.0
			39	9.0	14.1	7.0	8.2	10.6	7.9
			40	13.7	12.1	11.7	13.8	10.7	10.9
11	166	5	41	8.9	12.7	12.0	9.7	9.4	9.9
			42	9.4	13.4	10.6	12.1	9.8	10.1
			43	13.3	8.9	10.3	12.2	11.9	12.5
			44	12.3	15.7	10.8	9.3	6.4	5.6
12	Morphine sulphate	5	45	11.6	>25.0	23.5	10.8	7.4	7.4
			46	10.9	>25.0	21.3	10.0	13.4	9.7
			47	11.8	21.1	13.0	8.7	12.0	11.0
			48	12.0	14.7	13.8	9.3	8.3	7.2

5.3. X-Ray Crystallography Data for Compound 210

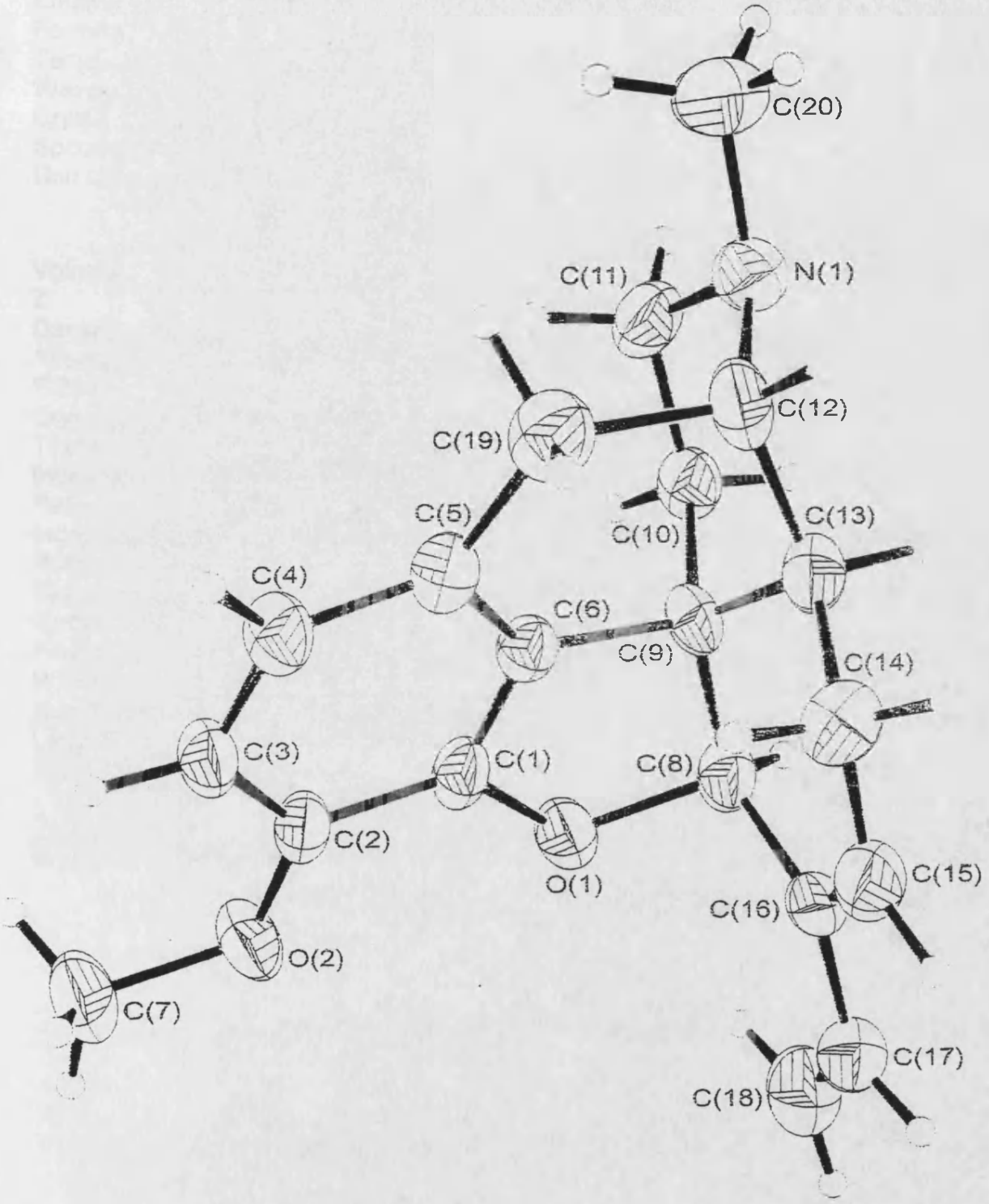
A crystal of approximate dimensions 0.4 x 0.3 x 0.3 mm was used for data collection.

Crystal data: $C_{20}H_{23}NO_2$, M = 309.39, Triclinic , a = 7.835(2), b = 8.402(4), c = 13.259(3) Å , α = 105.48(3), β = 94.63(2), γ = 94.93(2)°, U = 833.2(5) Å^3, space group $P1$, Z = 2, D_c = 1.233 gcm^{-3}, μ(Mo-K_α) = 0.079 mm^{-1}, F(000) = 332. Crystallographic measurements were made at 293(2)° K on a CAD4 automatic four-circle diffractometer in the range 2.53<θ<22.93°. Data (2515 reflections) were corrected for Lorentz and polarization but not for absorption.

The asymmetric unit was seen to consist of 2 molecules which are identical within the bounds of experimental error. In the final least squares cycles all atoms were allowed to vibrate anisotropically. Hydrogen atoms were included at calculated positions where relevant.

The solution of the structure (SHELX86)[1] and refinement (SHELX93)[2] converged to a conventional [i.e. based on 1380 F^2 data with $Fo>4\sigma(Fo)$] $R1$ = 0.0494 and $wR2$ = 0.1171. Goodness of fit = 1.029. The max. and min. residual densities were 0.172 and -0.193 eÅ^{-3} respectively. The asymmetric unit (shown in Fig. ...), along with the labelling scheme used was produced using ORTEX.[3] Final fractional atomic co-ordinates and isotropic thermal parameters, bond distances and angles are given in Tables ... , ... and ... respectively. Tables of anisotropic temperature factors are available as supplementary data.

1. Sheldrick G.M., Acta Cryst., A46, 467-73, 1990.
2. Sheldrick G.M., SHELXL, a computer program for crystal structure refinement, University of Göttingen, 1993.
3. McArdle P., J.Appl.Cryst., 27, 438, 1994


C(20)
N(1)
C(11)
C(12)
C(19)
C(10)
C(13)
C(5)
C(4)
C(6)
C(9)
C(14)
C(3)
C(1)
C(8)
C(2)
O(1)
C(15)
C(16)
O(2)
C(7)
C(17)
C(18)

Diene 210

Table 1. Crystal data and structure refinement

Empirical formula	$C_{20} H_{23} N O_2$
Formula weight	309.39
Temperature	293(2)°K
Wavelength	0.70930 Å
Crystal system	Triclinic
Space group	P1
Unit cell dimensions	a = 7.835(2)Å α = 105.48(3)°
	b = 8.402(4)Å β = 94.63(2)°
	c = 13.259(3)Å γ = 94.93(2)°
Volume	833.2(5) $Å^3$
Z	2
Density (calculated)	1.233 Mg/m^3
Absorption coefficient	0.079 mm^{-1}
F(000)	332
Crystal size	0.4 x 0.3 x 0.3 mm
Theta range for data collection	2.53 to 22.93 °.
Index ranges	0<=h<=8; -9<=k<=9; -14<=l<=14
Reflections collected	2515
Independent reflections	2515 [R(int) = 0.0000]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2505 / 3 / 420
Goodness-of-fit on F^2	1.029
Final R indices [$I>2\sigma(I)$]	R1 = 0.0494 wR2 = 0.1171
R indices (all data)	R1 = 0.1369 wR2 = 0.1844
Absolute structure parameter	3(4)
Largest diff. peak and hole	0.172 and -0.193 $eÅ^{-3}$
Weighting scheme	calc $w=1/[\sigma^2(Fo^2)+(0.0991P)^2+0.0000P]$
	where $P=(Fo^2+2Fc^2)/3$
Extinction coefficient	0.0014(49)
Extinction expression	$Fc^*=kFc[1+0.001xFc^2\lambda^3/\sin(2\theta)]^{-1/4}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
N(1)	5960(11)	10508(10)	-345(6)	66(2)
O(1)	7877(8)	5836(8)	1206(5)	64(2)
O(2)	6381(10)	5293(9)	2984(5)	72(2)
C(1)	6947(11)	6935(12)	1826(6)	56(2)
C(2)	6270(11)	6767(12)	2737(6)	53(2)
C(3)	5540(12)	8121(13)	3317(7)	60(3)
C(4)	5529(13)	9586(12)	3019(6)	60(3)
C(5)	6126(12)	9698(11)	2078(7)	58(2)
C(6)	6804(10)	8348(10)	1500(6)	47(2)
C(7)	5676(17)	5135(16)	3926(9)	91(4)
C(8)	8780(12)	6782(12)	557(7)	60(2)
C(9)	7625(12)	8128(13)	505(6)	57(3)
C(10)	6279(12)	7592(11)	-450(6)	58(2)
C(11)	5045(13)	8882(14)	-486(8)	71(3)
C(12)	7124(14)	11045(14)	628(8)	72(3)
C(13)	8535(12)	9846(13)	551(8)	63(3)
C(14)	9989(14)	10393(15)	1432(9)	81(3)
C(15)	11068(14)	9067(17)	1465(7)	74(3)
C(16)	10582(13)	7458(15)	1105(7)	65(3)
C(17)	11815(14)	6277(17)	1199(8)	74(3)
C(18)	11516(19)	4707(21)	964(10)	99(4)
C(19)	6273(15)	11235(14)	1682(8)	75(3)
C(20)	4830(17)	11737(16)	-447(10)	95(4)
N(1A)	9801(14)	4831(14)	8002(7)	94(3)
O(1A)	8079(9)	-1435(9)	6337(5)	73(2)
O(2A)	9745(10)	-3049(11)	4580(5)	83(2)
C(1A)	9014(12)	-586(13)	5750(7)	60(3)
C(2A)	9781(13)	-1382(14)	4848(8)	66(3)
C(3A)	10512(15)	-269(18)	4324(8)	83(3)
C(4A)	10442(16)	1412(17)	4653(8)	85(4)
C(5A)	9726(14)	2170(14)	5566(8)	71(3)
C(6A)	9080(12)	1084(14)	6101(7)	62(3)
C(7A)	10501(15)	-3838(18)	3660(9)	96(4)
C(8A)	7118(13)	-147(12)	6992(6)	66(3)
C(9A)	8214(12)	1496(14)	7094(7)	68(3)
C(10A)	9594(14)	1947(14)	8067(7)	77(3)
C(11A)	10749(16)	3482(18)	8086(8)	91(4)
C(12A)	8623(16)	4380(16)	7024(9)	84(3)

C(13A)	7273(15)	3001(15)	7104(9)	81(3)
C(14A)	5787(17)	2577(15)	6204(12)	103(4)
C(15A)	4765(17)	981(18)	6140(11)	94(4)
C(16A)	5326(12)	-255(16)	6454(8)	72(3)
C(17A)	4139(18)	-1774(20)	6312(10)	94(4)
C(18A)	4539(21)	-3089(22)	6489(12)	113(5)
C(19A)	9522(17)	3935(15)	5988(9)	83(3)
C(20A)	10869(22)	6363(18)	8161(11)	127(6)

Table 3. Bond lengths [Å] and angles [°]

N(1)-C(20)	1.443(12)	N(1A)-C(20A)	1.43(2)
N(1)-C(11)	1.445(14)	N(1A)-C(11A)	1.43(2)
N(1)-C(12)	1.458(14)	N(1A)-C(12A)	1.47(2)
O(1)-C(1)	1.367(11)	O(1A)-C(1A)	1.397(11)
O(1)-C(8)	1.497(10)	O(1A)-C(8A)	1.495(12)
O(2)-C(2)	1.371(11)	O(2A)-C(2A)	1.348(13)
O(2)-C(7)	1.439(11)	O(2A)-C(7A)	1.425(13)
C(1)-C(6)	1.378(12)	C(1A)-C(6A)	1.350(13)
C(1)-C(2)	1.393(11)	C(1A)-C(2A)	1.413(13)
C(2)-C(3)	1.388(13)	C(2A)-C(3A)	1.41(2)
C(3)-C(4)	1.390(13)	C(3A)-C(4A)	1.37(2)
C(4)-C(5)	1.390(12)	C(4A)-C(5A)	1.39(2)
C(5)-C(6)	1.364(12)	C(5A)-C(6A)	1.384(14)
C(5)-C(19)	1.518(14)	C(5A)-C(19A)	1.47(2)
C(6)-C(9)	1.489(12)	C(6A)-C(9A)	1.502(13)
C(8)-C(9)	1.520(14)	C(8A)-C(9A)	1.529(14)
C(8)-C(16)	1.523(14)	C(8A)-C(16A)	1.507(14)
C(9)-C(13)	1.538(13)	C(9A)-C(13A)	1.51(2)
C(9)-C(10)	1.521(13)	C(9A)-C(10A)	1.556(14)
C(10)-C(11)	1.521(13)	C(10A)-C(11A)	1.50(2)
C(12)-C(13)	1.55(2)	C(12A)-C(13A)	1.53(2)
C(12)-C(19)	1.572(14)	C(12A)-C(19A)	1.57(2)
C(13)-C(14)	1.51(2)	C(13A)-C(14A)	1.54(2)
C(14)-C(15)	1.46(2)	C(14A)-C(15A)	1.48(2)
C(15)-C(16)	1.32(2)	C(15A)-C(16A)	1.31(2)
C(16)-C(17)	1.46(2)	C(16A)-C(17A)	1.47(2)
C(17)-C(18)	1.27(2)	C(17A)-C(18A)	1.25(2)

C(20)-N(1)-C(11)	112.8(10)	C(20A)-N(1A)-C(11A)	113.3(13)
C(20)-N(1)-C(12)	112.4(9)	C(20A)-N(1A)-C(12A)	113.4(12)
C(11)-N(1)-C(12)	112.1(7)	C(11A)-N(1A)-C(12A)	111.2(9)
C(1)-O(1)-C(8)	105.8(7)	C(1A)-O(1A)-C(8A)	104.3(7)
C(2)-O(2)-C(7)	117.1(8)	C(2A)-O(2A)-C(7A)	118.3(9)
O(1)-C(1)-C(6)	112.9(7)	C(6A)-C(1A)-O(1A)	113.9(8)
O(1)-C(1)-C(2)	126.2(8)	O(1A)-C(1A)-C(2A)	123.8(9)
C(6)-C(1)-C(2)	120.8(8)	C(6A)-C(1A)-C(2A)	122.3(8)
O(2)-C(2)-C(1)	117.6(8)	O(2A)-C(2A)-C(1A)	118.8(8)
O(2)-C(2)-C(3)	125.8(7)	O(2A)-C(2A)-C(3A)	127.6(10)
C(1)-C(2)-C(3)	116.7(8)	C(1A)-C(2A)-C(3A)	113.5(10)
C(4)-C(3)-C(2)	121.6(8)	C(4A)-C(3A)-C(2A)	122.8(10)
C(5)-C(4)-C(3)	120.8(8)	C(3A)-C(4A)-C(5A)	122.4(10)

C(6)-C(5)-C(4)	117.1(8)	C(4A)-C(5A)-C(6A)	114.5(11)
C(6)-C(5)-C(19)	116.2(7)	C(6A)-C(5A)-C(19A)	117.5(9)
C(4)-C(5)-C(19)	126.4(8)	C(4A)-C(5A)-C(19A)	128.0(9)
C(5)-C(6)-C(1)	122.7(7)	C(1A)-C(6A)-C(5A)	124.1(9)
C(5)-C(6)-C(9)	129.5(8)	C(5A)-C(6A)-C(9A)	127.7(10)
C(1)-C(6)-C(9)	107.6(7)	C(1A)-C(6A)-C(9A)	108.0(9)
O(1)-C(8)-C(9)	103.4(7)	O(1A)-C(8A)-C(9A)	104.3(7)
O(1)-C(8)-C(16)	108.6(7)	O(1A)-C(8A)-C(16A)	109.4(7)
C(9)-C(8)-C(16)	113.6(9)	C(16A)-C(8A)-C(9A)	113.7(9)
C(6)-C(9)-C(8)	102.1(7)	C(6A)-C(9A)-C(13A)	107.5(8)
C(6)-C(9)-C(10)	111.1(8)	C(6A)-C(9A)-C(8A)	101.4(8)
C(8)-C(9)-C(10)	112.3(8)	C(13A)-C(9A)-C(8A)	117.3(9)
C(6)-C(9)-C(13)	105.9(7)	C(6A)-C(9A)-C(10A)	109.8(8)
C(8)-C(9)-C(13)	116.5(8)	C(13A)-C(9A)-C(10A)	108.7(9)
C(10)-C(9)-C(13)	108.6(7)	C(8A)-C(9A)-C(10A)	111.7(8)
C(11)-C(10)-C(9)	113.2(8)	C(11A)-C(10A)-C(9A)	110.2(9)
N(1)-C(11)-C(10)	111.5(8)	N(1A)-C(11A)-C(10A)	112.4(11)
N(1)-C(12)-C(13)	108.3(8)	N(1A)-C(12A)-C(13A)	107.0(9)
N(1)-C(12)-C(19)	116.5(9)	N(1A)-C(12A)-C(19A)	114.9(10)
C(13)-C(12)-C(19)	110.8(8)	C(13A)-C(12A)-C(19A)	113.6(10)
C(14)-C(13)-C(9)	111.4(8)	C(9A)-C(13A)-C(14A)	110.8(9)
C(14)-C(13)-C(12)	114.3(9)	C(12A)-C(13A)-C(14A)	112.8(9)
C(9)-C(13)-C(12)	106.8(8)	C(9A)-C(13A)-C(12A)	106.7(9)
C(15)-C(14)-C(13)	112.2(10)	C(15A)-C(14A)-C(13A)	111.4(11)
C(16)-C(15)-C(14)	126.0(10)	C(16A)-C(15A)-C(14A)	125.9(12)
C(15)-C(16)-C(17)	119.6(11)	C(15A)-C(16A)-C(17A)	118.8(12)
C(15)-C(16)-C(8)	121.8(9)	C(15A)-C(16A)-C(8A)	122.3(11)
C(17)-C(16)-C(8)	118.6(11)	C(17A)-C(16A)-C(8A)	118.9(12)
C(18)-C(17)-C(16)	127.2(12)	C(18A)-C(17A)-C(16A)	126(2)
C(5)-C(19)-C(12)	115.6(8)	C(5A)-C(19A)-C(12A)	115.3(9)

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^3$).
The anisotropic displacement factor exponent takes the form:
$-2\ pi^2\ [\ h^2\ a^*\ 2\ U11 + ... + 2\ h\ k\ a^*\ b^*\ U12\ ]$

Atom	U11	U22	U33	U23	U13	U12
N(1)	68(5)	82(6)	54(5)	24(4)	11(4)	21(5)
O(1)	71(4)	71(4)	57(4)	26(3)	19(3)	13(3)
O(2)	94(5)	72(4)	62(4)	35(4)	26(4)	11(4)
C(1)	41(5)	84(7)	36(5)	6(5)	8(4)	1(5)
C(2)	42(5)	71(7)	42(5)	10(5)	9(4)	-1(5)
C(3)	56(6)	84(7)	41(5)	18(5)	14(4)	3(5)
C(4)	67(6)	70(7)	37(5)	3(4)	14(4)	11(5)
C(5)	51(5)	64(6)	56(6)	11(5)	11(5)	2(5)
C(6)	44(5)	53(6)	42(5)	9(4)	8(4)	5(4)
C(7)	104(9)	108(9)	79(8)	49(7)	36(7)	14(7)
C(8)	55(6)	76(6)	51(5)	19(5)	19(5)	8(5)
C(9)	63(6)	78(6)	37(4)	24(4)	16(4)	8(5)
C(10)	57(6)	75(7)	38(5)	10(4)	7(4)	4(5)
C(11)	46(5)	102(9)	63(6)	21(6)	5(5)	10(6)
C(12)	74(7)	81(7)	72(7)	37(6)	28(6)	2(6)
C(13)	52(6)	78(7)	64(6)	29(5)	15(5)	0(5)
C(14)	57(6)	100(8)	91(8)	35(7)	8(6)	4(6)
C(15)	55(6)	112(10)	54(6)	27(6)	3(5)	-4(7)
C(16)	58(6)	105(9)	51(5)	41(6)	23(5)	30(6)
C(17)	61(7)	100(10)	66(7)	30(6)	11(5)	9(6)
C(18)	97(10)	121(12)	93(9)	41(8)	35(8)	23(9)
C(19)	76(7)	81(7)	64(6)	10(5)	13(5)	14(6)
C(20)	88(9)	115(10)	97(8)	47(7)	13(7)	42(8)
N(1A)	88(7)	102(8)	72(6)	-2(5)	25(6)	-29(6)
O(1A)	68(5)	91(5)	67(4)	28(4)	21(4)	7(4)
O(2A)	86(5)	107(6)	61(4)	23(4)	22(4)	18(4)
C(1A)	51(6)	85(8)	49(6)	25(5)	6(5)	5(5)
C(2A)	54(6)	88(8)	63(6)	30(6)	7(5)	10(5)
C(3A)	80(8)	124(11)	55(6)	37(7)	21(6)	17(7)
C(4A)	92(8)	115(11)	58(7)	39(7)	20(6)	-2(8)
C(5A)	67(6)	91(8)	54(6)	26(6)	7(5)	-11(6)
C(6A)	57(6)	84(8)	46(5)	19(5)	-1(5)	4(5)
C(7A)	68(7)	140(11)	76(8)	16(7)	19(6)	19(7)
C(8A)	72(7)	92(7)	31(4)	11(5)	13(5)	4(6)
C(9A)	48(6)	106(9)	49(6)	21(5)	7(5)	-1(6)
C(10A)	76(7)	113(9)	38(5)	13(5)	14(5)	7(7)
C(11A)	78(8)	136(11)	48(6)	13(6)	9(6)	-8(8)
C(12A)	81(8)	84(8)	81(8)	16(6)	10(7)	-1(6)

C(13A)	62(7)	97(9)	81(7)	20(6)	11(6)	3(6)
C(14A)	84(8)	73(8)	138(12)	25(8)	-33(8)	0(7)
C(15A)	66(7)	105(10)	106(9)	21(8)	2(7)	20(7)
C(16A)	42(6)	104(9)	56(6)	1(6)	11(5)	-10(6)
C(17A)	87(9)	113(10)	80(8)	17(8)	31(7)	11(9)
C(18A)	105(11)	112(12)	111(11)	14(9)	37(9)	-14(9)
C(19A)	92(8)	86(9)	65(6)	18(6)	4(6)	-16(6)
C(20A)	136(13)	116(11)	97(9)	-14(8)	39(9)	-52(9)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3)

Atom	x	y	z	U(eq)
H(3)	5047(12)	8046(13)	3920(7)	72
H(4)	5117(13)	10502(12)	3454(6)	72
H(7A)	6096(92)	6094(56)	4499(18)	136
H(7B)	6020(99)	4155(64)	4090(41)	136
H(7C)	4441(17)	5049(112)	3818(25)	136
H(8)	8846(12)	6058(12)	-151(7)	72
H(10A)	6860(12)	7375(11)	-1084(6)	70
H(10B)	5622(12)	6563(11)	-443(6)	70
H(11A)	4337(13)	8551(14)	-1158(8)	85
H(11B)	4289(13)	8933(14)	64(8)	85
H(12)	7702(14)	12140(14)	657(8)	86
H(13)	9027(12)	9763(13)	-116(8)	76
H(14A)	10697(14)	11339(15)	1341(9)	97
H(14B)	9510(14)	10745(15)	2099(9)	97
H(15)	12201(14)	9388(17)	1767(7)	89
H(17)	12941(14)	6728(17)	1460(8)	89
H(18A)	10412(19)	4190(21)	700(10)	119
H(18B)	12402(19)	4072(21)	1056(10)	119
H(19A)	6940(15)	12133(14)	2225(8)	90
H(19B)	5127(15)	11560(14)	1581(8)	90
H(20A)	5483(28)	12812(23)	-272(71)	142
H(20B)	3955(75)	11750(84)	21(55)	142
H(20C)	4299(93)	11466(65)	-1159(21)	142
H(3A)	11064(15)	-697(18)	3732(8)	99
H(4A)	10887(16)	2072(17)	4253(8)	103
H(7A1)	10141(94)	-5010(23)	3463(42)	145
H(7A2)	11734(15)	-3650(96)	3802(23)	145
H(7A3)	10139(93)	-3384(80)	3096(21)	145
H(8A)	7056(13)	-328(12)	7689(6)	79
H(10C)	9029(14)	2138(14)	8706(7)	92
H(10D)	10278(14)	1029(14)	8037(7)	92
H(11C)	11513(16)	3820(18)	8737(8)	109
H(11D)	11455(16)	3225(18)	7507(8)	109
H(12A)	8016(16)	5350(16)	7018(9)	101
H(13A)	6792(15)	3356(15)	7778(9)	97
H(14C)	5042(17)	3458(15)	6321(12)	123
H(14D)	6258(17)	2510(15)	5541(12)	123
H(15A)	3622(17)	840(18)	5850(11)	113
H(17A)	2996(18)	-1752(20)	6071(10)	112

H(18C)	5669(21)	-3164(22)	6731(12)	135
H(18D)	3706(21)	-3994(22)	6379(12)	135
H(19C)	8858(17)	4289(15)	5454(9)	100
H(19D)	10653(17)	4565(15)	6120(9)	100
H(20D)	10159(24)	7234(38)	8145(98)	191
H(20E)	11616(120)	6257(55)	7613(59)	191
H(20F)	11550(116)	6627(79)	8831(47)	191